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THE Q_1 DEFLECTION OF THE ELECTROCARDIOGRAM IN BUNDLE BRANCH BLOCK AND AXIS DEVIATION

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IT IS the purpose of this article to present and discuss observations on the incidence, in standard Lead I, of QRS complexes which display an initial downward deflection, or Q wave.

At the beginning of this study, we examined the tracings taken in 169 cases of bundle branch block. In all of these, the QRS interval measured 0.12 second, or more, and pronounced slurring or notching of the broadest QRS component was present. In 92 cases, there was no S wave in Lead I; these were classified as left branch block. The remaining 77 cases, in which there was a conspicuous S deflection in Lead I, were considered characteristic of right branch block. In 84, or 91.3 per cent, of the cases of left branch block, the first and only QRS component in Lead I was a broad R wave; in the remaining 8 cases (8.7 per cent), a small initial downstroke preceded this deflection (Table I). In the same group of cases, there were 33, or 35.9 per cent, in which the QRS complex of Lead III began with a downstroke, and these included one of the 8 which displayed a Q wave in Lead I. A Q_1 deflection was present in 34, or 44.2 per cent, and absent in 43, or 55.9 per cent, of the cases of right branch block. The QRS complex of Lead III began with a downstroke in 36.4 per cent of the cases of this group.

These observations on the incidence of Q_1 in bundle branch block were confirmed by examination of the tracings obtained in a group of cases of bundle branch block in which the conduction defect was present on one examination, but absent on an earlier or later occasion.

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TABLE I

THE FREQUENCY OF Q_1 AND Q_3 IN THE ELECTROCARDIOGRAMS OF 169 PATIENTS WITH BUNDLE BRANCH BLOCK

	LEFT BUNDLE BRANCH BLOCK		RIGHT BUNDLE BRANCH BLOCK	
	NUMBER OF PATIENTS	PERCENTAGE	NUMBER OF PATIENTS	PERCENTAGE
Q_1 present	8	8.7	34	44.2
Q_1 absent	84	91.3	43	55.9
Q_3 present	33	35.9	28	36.4
Q_3 absent	58	64.1	49	63.6
Q_1 and Q_3 present	1	1.1	11	14.3
Q_1 and Q_3 absent	52	56.5	26	33.8
Total	92		77	

TABLE II

THE EFFECT OF DEVELOPMENT OF BUNDLE BRANCH BLOCK ON THE Q WAVE IN LEAD I IN 102 PATIENTS SHOWING, AT ONE TIME, BUNDLE BRANCH BLOCK, AND, AT ANOTHER, NORMAL CONDUCTION

	LEFT BUNDLE BRANCH BLOCK		RIGHT BUNDLE BRANCH BLOCK	
	NUMBER OF PATIENTS	PERCENTAGE	NUMBER OF PATIENTS	PERCENTAGE
Q_1 present. Normal conduction	20	25.3	8	34.8
Q_1 absent. Normal conduction	59	74.7	15	65.2
Q_1 present. Bundle branch block	4	5.1	8	34.8
Q_1 absent. Bundle branch block	75	94.9	15	65.2
Q_1 absent, with and without block	57	72.1	14	60.9
Q_1 disappeared, with block	18	22.8 (of total) 90.0 (of those with Q_1)	1	4.3 (of total) 12.5 (of those with Q_1)
Q_1 appeared, with block	2	2.5 (of total) 3.4 (of those without Q_1)	1	4.3 (of total) 6.6 (of those without Q_1)
Q_1 with and without block	2	2.5 (of total) 10.0 (of those with Q_1)	7	30.4 (of total) 87.5 (of those with Q_1)
Total	79		23	

In our own files, we found 9 cases of this kind in which the block was on the left side, and 10 cases in which it was on the right side. By searching the literature, we collected 70 additional cases of the first sort and 13 of the second.[1-55] We did not include in this series any cases of the Wolff-Parkinson-White syndrome, nor any cases in which the QRS interval measured less than 0.12 second when the block was present, or more than 0.10 when it was absent. The incidence of Q_1 and other data relating to the 79 cases of left and 23 cases of right branch block assembled in this way are given in Table II. In 20 of the 79 cases of the first group, the QRS complex of Lead I began with a downstroke when intraventricular conduction was normal, and in all but two of these it began with an upstroke when left branch block was

TABLE III

INCIDENCE OF Q_1 IN PATIENTS WITH LEFT BUNDLE BRANCH BLOCK, RIGHT BUNDLE BRANCH BLOCK, LEFT AXIS DEVIATION, AND RIGHT AXIS DEVIATION

	LEFT BUNDLE BRANCH BLOCK		RIGHT BUNDLE BRANCH BLOCK		LEFT AXIS DEVIATION		RIGHT AXIS DEVIATION	
	NUMBER OF PATIENTS	PERCENTAGE	NUMBER OF PATIENTS	PERCENTAGE	NUMBER OF PATIENTS	PERCENTAGE	NUMBER OF PATIENTS	PERCENTAGE
Q_1 present	13	7.3	41	41	175	58.3	6	6
Q_1 absent	164	92.7	59	59	125	41.7	94	94
Total	177		100		300		100	

TABLE IV

Q_1 RELATIONSHIPS IN PATIENTS WITH LEFT BUNDLE BRANCH BLOCK AND LEFT AXIS DEVIATION (CONSECUTIVE CASES)

TYPE OF ELECTROCARDIOGRAM	Q_1 PRESENT	Q_1 ABSENT	TOTAL
Left axis deviation			
Index 24 or less	51	49	100
Index 25 or more	62	38	100
Normal T waves	69	31	100
Inverted T_1 or T_1 and T_2	55	45	100
Questionable left bundle branch block (QRS = 0.10 to 0.12)	46 (42.6%)	62 (57.4%)	108
Left bundle branch block	8 (8.7%)	84 (91.3%)	92

present. In the other 59 cases, the QRS complex of Lead I began with an upstroke when intraventricular conduction was normal; in 2 of these it displayed a Q wave when the left limb of the His bundle was blocked. As in the cases of left bundle branch block previously analyzed, the incidence of a Q_1 deflection was very low; it occurred in the presence of block in only 4 cases, or 5.1 per cent of the group. There was a Q_1 deflection with normal intraventricular conduction in 8 of the 23 cases of the second group, which is rather small for statistical purposes; in 7 of these, this deflection was likewise present when the right bundle branch failed to conduct. In the remaining 15 cases, Q_1 was absent with normal intraventricular conduction; in one of these, this deflection appeared when the right branch of the bundle was blocked.

The foregoing observations led us to compare the incidence of Q_1 in simple axis deviation with its incidence in bundle branch block. The ventricular complexes which depict simple left axis deviation and those which represent left branch block are often very similar in general contour, but our observations indicate that the electrocardiographic changes in these two conditions are fundamentally different in origin (Table III). With regard to the incidence of Q_1, left branch block is very different from simple left axis deviation (Table III). The relatively great frequency of a conspicuous Q_1 in simple left axis deviation, as compared to left branch block, is not materially affected by the criteria employed in the selection of examples of the former (Table IV). A Q_1 deflection was present in 51 of 100 cases of simple

TABLE V

Q-WAVE RELATIONSHIPS IN PATIENTS WITH RIGHT BUNDLE BRANCH BLOCK AND RIGHT AXIS DEVIATION

TYPE OF ELECTROCARDIOGRAM	Q_1 PRESENT		Q_3 PRESENT		Q_1 AND Q_3 PRESENT		NO Q		TOTAL
	NUMBER	PERCENTAGE	NUMBER	PERCENTAGE	NUMBER	PERCENTAGE	NUMBER	PERCENTAGE	
Right axis deviation	6	6.0	81	81.0	2	2.0	15	15.0	100
Right bundle branch block	34	44.2	28	36.4	11	14.3	26	33.8	77

left axis deviation in which the axis deviation index $(R_1 + S_3) - (R_3 + S_1)$, was 24 or less, and in 62 of 100 cases of left axis deviation in which this index exceeded 24. This deflection was present in 69 of a series of 100 consecutive cases of simple left axis deviation with normal T waves, and in 55 of 100 consecutive cases of the same kind in which the T waves were inverted in Lead I or in Leads I and II. It is of particular interest that Q_1 was present in 42.6 per cent of a series of 108 cases, all that could be found in a file of 8,000 electrocardiograms, in which definite left axis deviation was associated with a QRS interval of 0.10 to 0.12 second. With respect to the incidence of this deflection, electrocardiograms of this kind resemble those which depict simple left axis deviation, and are quite unlike those which represent left bundle branch block.

In simple right axis deviation, the frequency of Q_1 is very small, about the same as in left branch block, whereas, in right branch block, the frequency of this deflection is not very different from its frequency in left axis deviation (Tables I and V). The incidence of Q_3 is very high in right axis deviation and relatively low in right bundle branch block.

DISCUSSION

The incidence of Q_1 in bundle branch block has received little attention in the literature. Many years ago, Willius[56] recorded the size of the different QRS components in 99 examples of left branch block. His tables show that Q_1 was present in only two of his cases, but he did not comment upon this infrequency. In 1916, Lewis[57] was under the impression that Q_1 was usually present in bundle branch block of the common type; in 1924 he spoke of it as appearing to a variable extent.[58] In 1931, Wilson, Macleod, and Barker[59] stated that, in left branch block, Q is almost always present in Lead I and absent in Lead III. This statement was evidently based upon an impression, rather than upon the examination of an adequate series of cases.

With regard to the frequency of a Q_1 deflection, the curves that represent canine branch block are quite different from those that represent human branch block. In 6 of Lewis' experiments on dogs, Q_1 became larger; in two, it disappeared; and, in one, it persisted un-

changed when the left bundle branch was cut. In the remainder, it was absent both before and after section of this tract. A Q_1 deflection was present in four and absent in two of six examples of canine left branch block studied by Wilson and Herrmann.[60]

The rarity of Q_1 in human left branch block and the pronounced tendency for this deflection to disappear when left branch block develops clearly indicate that, in the vast majority of human electrocardiograms, it represents electrical forces originating in left ventricular muscle, or at least in muscle which receives the excitatory impulse by way of the left Purkinje plexus. The relatively high frequency of Q_1 in right branch block, and the tendency for this deflection to persist when normal conduction gives place to this disturbance, point in the same direction. Lewis, believing that the incidence of Q_1 was high in bundle branch block of the common type and, at the same time, that this kind of block was due to a conduction defect in the right bundle branch, arrived at the correct conclusion—that this deflection was contributed to the human bicardiogram by the levocardiogram. This is an instance in which the conclusion was valid even though the premises were erroneous.

Although it is clear that Q_1 usually represents electrical forces produced by the activation of left ventricular muscle, direct evidence as to the exact manner of its origin is not available. In experiments on dogs, endocardial readings have been employed in an attempt to locate the regions of ventricular muscle which are first to pass into the active state, but the data obtained in this way are of comparatively little value for the purpose of ascertaining the origin of the earliest QRS component of the human electrocardiogram. In the first place, the incidence of Q_1 is by no means the same in canine as in human curves, and, in the second, endocardial readings are not entirely trustworthy, as Wilson, Macleod, and Barker have pointed out. Even if the ventricular point which is activated earliest were known, we could not feel certain that Q_1 is written by events occurring in its neighborhood, for the electrical forces developed in this region may be overbalanced by the more rapid development of opposing forces somewhere else before they become large enough to produce a potential difference between the distant electrodes on the two arms.

The activation of left ventricular muscle may give rise to a Q_1 deflection by producing initial positivity of the right arm, initial negativity of the left arm, or both. In normal subjects, initial negativity of the anterolateral surface of the left ventricle often produces a Q deflection in leads from the left side of the precordium, and is frequently transmitted to the left arm as well. This negativity is transmitted to the epicardial surface from the ventricular cavity when the subendocardial muscle of the anterolateral wall enters the active state later, or produces electrical forces of less magnitude than the

subendocardial muscle on the opposite side of the left ventricle. It may, therefore, be ascribed to unbalanced forces produced by the spread of the excitatory impulse into the septum from the left Purkinje plexus. These same forces and, also, those generated by activation of the free wall of the right ventricle from within outward produce initial positivity of the epicardial surface on the right side of the heart, which gives rise to small R waves in leads from the right side of the precordium and is sometimes transmitted to the right arm. The absence of Q_1 in the vast majority of the cases of human left branch block appears, therefore, to be due to the absence of electrical forces normally produced by the activation of septal muscle from left to right.

What is the significance of Q_1 in the small percentage of cases of human left branch block in which it occurs? In left branch block, no left ventricular muscle is undergoing activation at the beginning of the QRS interval, and, if a Q deflection is present, it must be ascribed to forces of right ventricular origin. Under certain circumstances the initial positivity of the surface of the right ventricle due to the outward spread of the impulse through its free wall, which usually gives rise to small R waves in leads from the right side of the precordium in left branch block, may be transmitted to the right arm and thus give rise to a Q_1 deflection. It is apparent that this often happens in the dog and seldom happens in man. In the former, the long axis of the heart is much more nearly in line with the long axis of the body, and this may account for the difference in the frequency of Q_1 between canine and human left branch block. Rotation and elevation of the heart after section of the left bundle branch have caused a Q_1 deflection to appear in experiments on the dog, but not in experiments on the monkey, an animal in which the heart, with regard to its position, is more like that of man.[61] No peculiarities in the position of the heart were noted in the thirteen cases of left branch block in our series in which a Q_1 deflection was present. Both in the dog and in man, the presence of a Q_1 deflection, when the left branch of the His bundle is blocked, may, of course, depend upon some factor other than the position of the heart. A possibility that must be considered is that it is due to some peculiarity of the Purkinje system or the architecture of the subdivisions of the bundle branches, and consequently of the order of ventricular activation. In two instances, it was noted that a Q_1 deflection was present both before and after the development of left branch block, and had the same contour in both tracings. There exists, then, the possibility that in some instances the distribution of the conducting tracts is such as to lead to more rapid or earlier activation of those parts of the right ventricular muscle which produce forces of the kind that give rise to a Q_1 deflection, and that under these circumstances this deflection occurs and displays the same form in both bicardiogram and dextrocardiogram. This would account for the rare cases in which Q_1 disappears when right branch block develops.

In order to ascertain whether the presence of a Q_1 deflection in left bundle branch block has any diagnostic significance, we reviewed the histories of the thirteen patients in our own series and twenty-four cases found in the literature which presented this combination. An autopsy was performed in only two of our own cases. One of these was that of a man, aged 51 years, and in this instance the right coronary artery was occluded and the posterior ventricular wall was infarcted; the ventricular septum was not involved. In the second case, that of a man aged 56 years, there were pronounced cardiac hypertrophy, moderate coronary sclerosis, and slight fibrosis and patchy fatty degenerative infiltration of the myocardium. No macroscopic, circumscribed, septal lesions were found. In the remaining eleven cases, the following clinical diagnoses were made: arteriosclerotic heart disease with questionable coronary occlusion in two; coronary occlusion in five, in one of which left branch block antedated the symptoms pointing to infarction; arteriosclerotic heart disease with congestive failure in two; and rheumatic heart disease with mitral stenosis and aortic insufficiency in two.

The data relating to the conditions present in the twenty-four cases found in the literature are meager.[8, 22, 25, 32, 36, 41, 54, 56, 57, 62-70] In eight instances, no details of any kind were given as to the nature of the cardiac lesions. One patient had arteriosclerotic heart disease, cardiac enlargement, aortic insufficiency, and congestive failure. This patient died, but was not autopsied. Another had pericarditis with effusion and recovered; a third was said to have myocardial degeneration; a fourth, auricular fibrillation with congestive failure; a fifth, mitral stenosis; a sixth, aortic insufficiency; a seventh, diphtheria; an eighth, arteriosclerotic heart disease with failure. The ninth and tenth were reported as cases of coronary thrombosis in which the clinical diagnosis was confirmed by electrocardiographic examination; both of these patients recovered.

The remaining six patients died and were subjected to autopsy. The ventricular septum was involved in all. In one instance, there was occlusion of the anterior descending coronary artery, with infarction involving the anterior and part of the posterior wall of the left ventricle, the septum, and the apex. The interventricular septum was almost completely infarcted and in a state of liquefaction necrosis.[54] In another case there was thrombosis of an artery supplying the septum, with myocardial infarction and serofibrinous pericarditis.[66] In a third there was anterior infarction involving the septum.[32] The fourth was one with multiple infarcts; the lower, anterior part of the interventricular septum was involved.[70] In the fifth, described in the same report[70] as the fourth, a diagnosis of hypertensive heart disease with congestive failure was made, and moderate sclerosis of the coronary arteries was found post mortem. Histologic studies disclosed small scars in the myocardium, including a few in the septum, but the bulk

of the heart muscle appeared to be in good condition. In the sixth and last case,[63] the QRS interval measured only 0.107 second, but the precordial electrocardiogram indicated that activation of the left ventricle was delayed. At autopsy there was no cardiac hypertrophy; a healed infarct was found. It involved the entire apex, the apical four-fifths of the anterior and lateral walls of the left ventricle, and apical four-fifths of the anterior two-thirds of the interventricular septum.

From these few data, no very definite conclusions can be drawn. The heart was examined post mortem in only eight of the thirty-seven cases of left branch block with a Q_1 deflection which we were able to collect. It may be significant that, in six of these, myocardial infarction had occurred, and that, in five of the six and in one additional case, septal lesions were present. On the other hand, the cardiac abnormalities diagnosed clinically in many of the remaining twenty-nine cases in which there was no autopsy are not of a kind in which septal involvement would be expected. Even when bundle branch block is found after the occurrence of symptoms and physical signs characteristic of coronary thrombosis, one cannot feel certain that a large amount of the ordinary muscle of the ventricular septum has been infarcted. We know, however, that, in dogs, ligation of the septal artery, a large vessel not present in man, produces infarction of the basal part of the ventricular septum and often induces right bundle branch block or complete atrioventricular block.[71] Whether it ever induces left branch block alone is not certain. Right branch block produced in this way is sometimes, although not always, represented by ventricular complexes quite different in form from those obtained after section of the right branch of the His bundle.

On theoretical grounds, one might expect that, in left branch block, damage to the ventricular septum would lead to the appearance of a Q deflection in Lead I. In uncomplicated left branch block, the cavity of the right ventricle is negative throughout the QRS interval, but the cavity of the left is initially positive because of the direction of the electrical forces produced by activation of the septal muscle from right to left. This initial positivity is transmitted through the still inactive free wall of the left ventricle to the outer surface of this chamber and to the adjacent parts of the body, including the left side of the precordium, the left axilla, and, when the heart is in a relatively horizontal position, as in most patients with left branch block, to the left arm. Under these circumstances, the QRS complex of leads from the left side of the precordium display no Q deflection, and those of Lead I are of the same form. When the septum is extensively damaged, the electrical forces produced by its activation are reduced or abolished, and the initial negativity of the right ventricular cavity is transmitted to the left, and, consequently, to those regions on the left side of the body that are initially positive in left branch block when the septal

muscle is healthy. When this happens, Q deflections occur in leads from the left side of the precordium. They may be expected in Lead I also, although, in one case of this sort on record, large Q waves were present in leads from the left side of the precordium, but not in Lead I.[72]

From the data available, we cannot be sure that the mechanism in question gave rise to the Q_1 deflection in the cases of left branch block with septal lesions under consideration. In 2 of these, this deflection appeared after symptoms characteristic of coronary thrombosis had occurred, which suggests that infarction of the septum produced it. In another case, however, the Q_1 deflection antedated the coronary accident. The final decision as to whether there is a pronounced positive correlation between the presence of a Q_1 deflection in left branch block and septal involvement must wait until more extensive studies have been carried out. In the meantime, it is desirable that a full set of precordial leads be taken whenever a Q_1 deflection is encountered in tracings otherwise characteristic of left branch block, not only for the purpose of ascertaining whether left branch block is really present, but also to find out whether a Q deflection is present in leads from the left side of the precordium and left axilla.

It must be remembered that bundle branch block in man is almost always complicated by other cardiac abnormalities. The form of the electrocardiogram is determined not only by the failure of one bundle branch to conduct, but by extensive lesions of the ordinary ventricular muscle, as in infarction, and by involvement of other conducting tracts or the Purkinje network. Wilson and Herrmann[60] severed minor and major subdivisions of the left bundle branch in their experiments on dogs. In one instance, a cut on the left side of the septum, after the right branch of the His bundle had been divided, led to the appearance of a prominent Q_1 deflection. The possibility that the presence of Q_1 in left branch block is sometimes due to a combination of conduction defects must, therefore, be borne in mind.

The similarity in general contour between the ventricular electrocardiograms obtained in preponderant hypertrophy of the left ventricle and those characteristic of bundle branch block of the more common type has attracted attention for a great many years. Lewis, believing that the right branch of the His bundle was the one affected in bundle branch block of this type, brought forward a considerable body of evidence in support of the view that the ventricular complex was dominated by the levocardiogram in both conditions. Now that the block is known to be on the left side instead of the right, this view is no longer tenable.

The similarity in question involves the position of the mean electrical axis, the direction of rotation of the instantaneous electrical axis, the direction and sequence in time of the major QRS deflections of the different limb leads, and the form of the T waves, which are almost always inverted in Lead I in left bundle branch block and are very

often inverted in this lead in left ventricular hypertrophy. In many instances of great hypertrophy of the left ventricle, the QRS interval is increased to between 0.10 and 0.12 second, and, under such circumstances, it may be difficult to ascertain whether the electrocardiographic abnormalities are due to left ventricular hypertrophy alone or to incomplete left branch block.

Luten and Grove[35] and Hyman and Parsonnet[25] championed the view that pronounced left axis deviation with inversion of the T deflections in Lead I and upright T waves in Lead III is due to incomplete branch block, even when the QRS interval is not distinctly increased. Luten and Grove stressed the point that this conception was the only one that satisfactorily explained both the axis deviation and the form of the T waves. The anatomic arguments which they advanced to support it are no longer valid because they were based on the erroneous ideas concerning the diagnosis of right and left branch block which were current at the time their paper was written. In 1920, Fahr[73] put forward the hypothesis that the form of the ventricular complex in preponderant enlargement of the left ventricle is due to an increase in the length of the subdivisions of the left branch of the His bundle, and a consequent delay in the activation of the muscle of the left ventricle as compared to that of the right. At the same time he asserted that the classical views as to the location of the conduction defect in the two varieties of bundle branch block were erroneous, and that what had been considered right was really left branch block, and vice versa. Fahr's contention is clearly in accord with the observations of Luten and Grove and Hymen and Parsonnet, and supports the view that left axis deviation accompanied by inversion of the T waves in Lead I is the first stage, so to speak, in the development of left branch block; it also offers an alternative explanation of the tendency toward an increase in the QRS interval in left ventricular hypertrophy, attributed by Lewis to the increased thickness of the left ventricular wall.

The views regarding the cause of left axis deviation and inversion of the T deflections in Lead I in preponderant enlargement of the left ventricle held by Fahr are nearly, although not exactly, equivalent to the idea that these electrocardiographic changes are the result of incomplete left bundle branch block. Now, it is obvious that the initial QRS components in incomplete left branch block must be identical in form with those present in complete left branch block. In both cases these components represent the earliest phases of the dextrocardiogram, and there can be no reason why this should begin with a downward deflection in the one case and not in the other. It is for this reason that we have compared the incidence of Q_1 in axis deviation with its incidence in bundle branch block (Table IV). As we have already pointed out, this deflection is present in about one-half the cases of left axis deviation, and its frequency is nearly the same, regardless of whether we confine our attention to cases in which the

axis deviation index is very large or to cases in which it is only moderately increased, to cases in which the T waves are normal or to those in which the T waves are inverted in Lead I, or to cases in which the QRS interval lies within the accepted normal range or to those in which it measures between 0.10 and 0.12 second. On the other hand, Q_1 occurs in less than one-tenth of the cases of left bundle branch block. Contrary to what would be expected if left axis deviation were due to slow conduction of the cardiac impulse through the left limb of the His bundle, there is no tendency for the incidence of Q_1 to fall as the axis deviation index rises, or as the QRS interval lengthens. In order to obtain additional data bearing upon this problem, we reviewed all of the electrocardiograms taken in this laboratory over a period of three years with reference to the number of cases of left axis deviation in which Q_1 was the largest Q wave present in any of the limb leads; this information had been routinely coded. There were 1,199 cases of left axis deviation, and Q was largest in Lead I in 566, or 47.2 per cent of the total; Q was also largest in Lead I in 39 per cent of the 588 classified as showing slight left axis deviation, 54 per cent of the 611 classified as showing pronounced left axis deviation, and 40.4 per cent of 304 cases in which the T waves were inverted in Lead I and no digitalis had been given. In a review of curves of this last type, it was often noted, when a series of curves had been taken, that inversion of the T waves developed with the passage of time without any accompanying change in the contour of the QRS complex. These data show clearly that there is no justification for considering incomplete left branch block the sole, or even a common, cause of left axis deviation alone, or of left axis deviation associated with inversion of the T deflections in Lead I. For, if it were, we should certainly expect the incidence of Q_1 in left axis deviation to approach its incidence in complete left branch block as the form of the ventricular complex became more abnormal with respect to the value of the axis deviation index, the form of the T waves, or the length of the QRS interval.

We do not, of course, deny that left axis deviation, whether or not it is accompanied by inversion of T in Lead I, by an increase in the QRS interval, or by both, is sometimes due to incomplete left bundle branch block. When a Q deflection is present in Lead I, however, this is very unlikely, because the incidence of this deflection cannot be greater in incomplete than in complete left bundle branch block. When Q_1 is absent, the estimation of the probability that incomplete left branch block is or is not present is much more difficult. The probability that it is present is no doubt greater when the QRS interval measures between 0.10 and 0.12 second than when it is shorter. Since the incidence of Q_1 reached 42.6 per cent in the group of 108 cases of left axis deviation in which the QRS interval was more than 0.10 and less than 0.12 second in length and was no greater in those in which T_1 was inverted than in those in which it was upright, it seems prob-

able, however, that only a small percentage of the curves of this kind, in which Q_1 is absent, represent a conduction defect in the left limb of the His bundle.

In Lead III, the QRS complex begins with a downward deflection (Q or QS) in about one-third of the cases of left bundle branch block, and in approximately the same percentage of the cases of right branch block. In left branch block this deflection is not followed by a positive component, and should, therefore, be called QS instead of Q. Its presence may be due either to initial positivity of the left arm, to initial negativity of the left leg, or to both. The former is exceedingly common in left branch block because the initial positivity of the cavity of the left ventricle due to the spread of the cardiac impulse through the septal muscle from right to left is usually transmitted to the left arm. Were it not for the circumstance that the left leg is also initially positive in the majority of cases, because the initial positivity of the right ventricular surface due to the spread of the impulse through the free wall of the right ventricle is transmitted to it, a QS deflection would occur in Lead III almost as frequently as Q is absent in Lead I, and for the same reason. In a considerable percentage of the cases of left bundle branch block, the surface of the right ventricle is initially negative, as is shown by the absence of an R deflection in leads from the right side of the precordium, and in many of these this initial negativity is, no doubt, transmitted to the left leg and contributes to the frequency of a QS deflection in Lead III. It should be pointed out that these relations hold when the heart is in a relatively horizontal position. When the heart is relatively vertical, the potential of the left leg is like that at the left, instead of like that at the right, ventricular surface. In the dog, the long axis of the heart is nearly in line with the long axis of the trunk, and Q, or QS, deflections are very rare in Lead III in canine left branch block. In canine right branch block, on the other hand, Q_3 is present more often than absent.

In the kind of branch block curves that closely resemble those obtained in preponderant hypertrophy of the right ventricle with regard to the direction and relative size of the ventricular deflections of the standard limb leads, a Q_1 component very rarely occurs. Curves of this kind, which were at one time considered characteristic of left branch block, are very uncommon. In the great majority of the cases in which they occur, the precordial electrocardiogram is in every way typical of right branch block; in some instances, however, it indicates that the conduction defect is on the left side. Of the seventy-seven cases classified as right branch block in Table I, there were only seven in which the electrocardiograms were of this kind. In the other seventy cases, the QRS complex of Lead I displayed a narrow R wave which often attained a voltage equal to, or greater than, that of the broad, notched, or slurred S wave which followed it. The high incidence of Q_1 in right branch block is mainly due to the frequency of

this deflection in electrocardiograms of this type. When the heart is in a relatively horizontal position, as is usually the case when the patient has left axis deviation or bundle branch block, Q_1 is almost always of left ventricular origin, and its presence or absence is determined by the character of the potential variations at the surface of the left ventricle at the beginning of the QRS interval. In left branch block, it is rare because the potential of the left ventricular surface, and consequently of the left arm, is initially positive. In left axis deviation, it is present when these regions are initially negative and absent when they are initially positive. Since right bundle branch block does not materially affect the potential at the surface of the left ventricle early in the QRS interval, Q_1 persists, unchanged in form, or remains absent, as the case may be, when right branch block develops (Table II).

The rarity of Q_1 in right axis deviation cannot be explained in an entirely satisfactory manner at the present time. In normal persons who display this electrocardiographic peculiarity, the heart is usually in a vertical position. For this reason, initial negativity of the left ventricular surface is transmitted to the left leg, and produces Q deflections in Leads II and III instead of in Lead I. The potential of the left arm resembles that of the right ventricular surface, which is initially positive. In right ventricular hypertrophy the situation is different; the enlarged heart is ordinarily transversely placed. Usually, unlike right bundle branch block, right ventricular hypertrophy has a profound effect upon the potential at the surface of the left ventricle at the very beginning of the QRS interval. This condition is represented in the precordial electrocardiogram by tall R waves, often preceded by Q waves in leads from the right side of the precordium and by small R waves, followed by deep S waves, in leads from the left side of the precordium.[74] In right ventricular hypertrophy, therefore, Q deflections are of right ventricular origin, and depend upon the occurrence of initial negativity at the surface of the right ventricle. Since this initial negativity, when it occurs, is transmitted to the left leg and not to the left arm, which undergoes potential variations like those at the left ventricular surface, Q deflections, when present, appear in Leads II and III and not in Lead I. The data available at the present time afford no satisfactory explanation of the tendency for right ventricular hypertrophy to abolish initial negativity at the left ventricular surface or to induce initial negativity at the right ventricular surface. The solution of this problem must, therefore, be left to the future.

SUMMARY

An initial downward, or Q, deflection in Lead I is very uncommon in human left branch block. When this component occurs in an electrocardiogram otherwise characteristic of this conduction defect, a lesion

of the ordinary muscle of the ventricular septum should be suspected, and a full set of precordial leads should be taken.

A Q deflection in Lead I occurs in about one-half of all cases of left axis deviation, regardless of the criteria employed in selecting examples of this electrocardiographic abnormality. Left axis deviation accompanied by inversion of the T waves in Lead I may sometimes be due to incomplete left bundle branch block when Q_1 is absent, but it is almost never due to this cause when this deflection is present.

The incidence of Q_1 in right branch block is similar to its incidence in left axis deviation. In right axis deviation, this deflection is extremely rare.

REFERENCES

1. Bach, F.: On the Clinical Significance of Right Bundle Branch Block, Quart. J. Med. **23**: 261, 1930.
2. Baker, B. M.: The Effect of Cardiac Rate and the Inhalation of Oxygen on Transient Bundle Branch Block, Arch. Int. Med. **45**: 814, 1930.
3. Bishop, L. F., Jr.: Transient Recurrent Complete Left Bundle Branch Block, Am. Heart J. **15**: 354, 1938.
4. Bohnengel, C.: Paroxysmal Bundle Branch Block Associated With Physiologic Changes in a Patient With Organic Heart Disease, Am. Heart J. **16**: 587, 1938.
5. Bousfield, G.: Angina Pectoris: Changes in Electrocardiogram During Paroxysm, Lancet **2**: 457, 1918.
6. Campbell, M., and Suzman, S. S.: Simultaneous Disappearance of Gallop Rhythm and Bundle Branch Block, Lancet **1**: 985, 1932.
7. Carr, F. B.: Functional Bundle Branch Block, New England J. Med. **209**: 1101, 1933.
8. Carter, E. P.: Clinical Observations on Defective Conduction in the Branches of the Auriculo-Ventricular Bundle, Arch. Int. Med. **13**: 803, 1914.
9. Comeau, W. J., Hamilton, J. G. M., and White, P. D.: Paroxysmal Bundle Branch Block Associated With Heart Disease, Am. Heart J. **15**: 276, 1938.
10. Cowan, J., and Bramwell, J. C.: The Clinical Aspects of Bundle Branch Block, Quart. J. Med. **19**: 95, 1925.
11. Cutts, F. B., and Roberts, C. P.: Two-to-One and Three-to-One Left Bundle Branch Block in the Presence of Auricular Flutter, Am. Heart J. **15**: 501, 1938.
12. Digilio, V. A.: Reversible Bundle Branch Block in a Case of Toxic Goiter, Am. Heart J. **15**: 116, 1938.
13. Donath, F.: Über inkonstanten Schenkelblock und über die Wirkung von Corphyllamin auf das Herz, Ztschr. f. klin. Med. **132**: 802, 1937.
14. Dressler, W.: Atlas der klinischen Elektrokardiographie, Berlin und Wien, 1933, Urban & Schwarzenberg, Figs. 42 and 45.
15. Eidlow, S.: Transient, Recurrent Bundle Branch Block, Canad. M. A. J. **37**: 240, 1937.
16. Elliot, A. H., and Nuzum, F. R.: Bundle Branch Block With Periods of Normal Intraventricular Conduction: Report of an Unusual Case, Am. Heart J. **7**: 680, 1932.
17. Freundlich, J.: Über die Beeinflussung intraventrikularer Leitungsstörung durch den Carotisdruck, Deutsches Arch. f. klin. Med. **168**: 360, 1930.
18. Gilchrist, A. R., and Ritchie, W. J.: The Ventricular Complexes in Myocardial Infarction and Fibrosis, Quart. J. Med. **23**: 273, 1930.
19. Hart, T. S.: Block of the Branches of the Bundle of His, Arch. Int. Med. **35**: 115, 1925.
20. Herrmann, G., and Ashman, R.: Partial Bundle Branch Block: A Theoretical Consideration of Transient Normal Intraventricular Conduction in the Presence of Apparently Complete Bundle Branch Block, Am. Heart J. **6**: 375, 1931.
21. Hewlett, A. W.: A Case Showing Bundle Branch Block With Extrasystoles Originating in the Ventricular Septum, Heart **9**: 1, 1921.
22. Hill, I. G. W.: Bundle Branch Block: A Clinical and Histological Study. Quart J. Med. **24**: 15, 1930.

23. Horine, E. F.: Prognosis in Rheumatic, Hypertensive, and Syphilitic Heart Disease, Am. Heart J. **1**: 617, 1926.
24. Hubert, G.: Beobachtungen über einen Fall von ausheilendem rechteseitingem Schenkelblock, Ztschr. f. Kreislaufforsch. **27**: 449, 1935.
25. Hyman, A. S., and Parsonnet, A. E.: Bundle Branch Block. The Phenomenon of Its Development in Relation to Axis Deviation of the Heart, Arch. Int. Med. **45**: 868, 1930.
26. Kelly, L. W.: Two-to-One Right Bundle Branch Block, Am. Heart J. **6**: 285, 1930.
27. Keppel, C.: Über die Bedeutung der Elektrokardiographie für die Beurteilung von Diphtheriekranken, Jahrb. f. Kinderh. **147**: 171, 1936.
28. Korth, C., and Schrumpf, W.: Über Interferenzdissoziation in Elektrokardiogramm, Deutsches Arch. f. klin. Med. **179**: 321, 1936.
29. Krumbhaar, E. B.: Transient Heart Block—Electrocardiographic Studies, Arch. Int. Med. **19**: 750, 1917.
30. Kurtz, C. M.: Transient Complete Bundle Branch Block, Am. Heart J. **11**: 212, 1936.
31. Leinbach, R. F., and White, P. D.: Two-to-One Right Bundle Branch Block, Am. Heart J. **3**: 422, 1928.
32. Levine, S. A., and Brown, C. L.: Coronary Thrombosis: Its Various Clinical Features, Medicine **8**: 245, 1929.
33. Lewis, T.: Certain Physical Signs of Myocardial Involvement, Brit. M. J. **1**: 484, 1913.
34. Lewis, T.: Auricular Flutter Continuing for 24 Years, Brit. M. J. **1**: 1248, 1937.
35. Luten, D., and Grove, E.: The Incidence and Significance of Electrocardiograms Showing the Features of Left Axis Deviation and QRS of Normal Duration With Inverted T_1 and Upright T_3, Am. Heart J. **4**: 431, 1929.
36. Master, A. M., Dack, S., and Jaffe, H. L.: Bundle Branch and Intraventricular Block in Acute Coronary Artery Occlusion, Am. Heart J. **16**: 283, 1938.
37. Morris, R. S., and McGuire, J.: Transient Complete Bundle Branch Block, Am. J. M. Sc. **184**: 202, 1932.
38. Perry, C. B.: Observed Onset of Bundle Branch Block With Coronary Thrombosis 45 Hours Later, Am. Heart J. **9**: 677, 1934.
39. Pezzi, C.: Quelques remarques sur les troubles de la conductibilite intraventriculaire enregistres par l'electrocardiogramme, Arch. d. mal du cœur **18**: 753, 1925.
40. Pick, A.: Beitrag zur Frage des atypischen Schenkelblocks, Ztschr. f. klin. Med. **129**: 719, 1936.
41. Robinson, G. C.: The Relation of Changes in the Form of the Ventricular Complex of the Electrocardiogram to Functional Changes in the Heart, Arch. Int. Med. **18**: 830, 1916.
42. Schwab, R.: Klinische und elektrokardiographische Beobachtungen über vorübergehenden Schenkel—under Verzweigungsblock, Deutsches Arch. f. klin. Med. **180**: 664, 1937.
43. Slater, S. R.: Partial Bundle Branch Block. A Case of Three-to-One and Four-to-One Block, Am. Heart J. **5**: 617, 1930.
44. Stecher, R. M.: Electrocardiographic Changes in Diphtheria, Am. Heart J. **4**: 715, 1929.
45. Stenström, N.: An Experimental and Clinical Study of Incomplete Bundle Branch Block, Acta Med. Scandinav. **60**: 552, 1924.
46. Stenström, N.: Further Experience on Incomplete Bundle Branch Block in Man, Acta Med. Scandinav. **67**: 353, 1927.
47. Tung, C. L., and Cheer, S. N.: A Correlation of Clinical and Electrocardiographic Findings in Human Bundle Branch Block, Chinese M. J. **47**: 15, 1933.
48. Viko, L. E., Marvin, H. M., and White, P. D.: A Clinical Report on the Use of Quinidine Sulphate, Arch. Int. Med. **31**: 345, 1923.
49. von Mentzingen, A.: Über einen Fall von funktionellen Verzweigungblock, Klin. Wchnschr. **13**: 1158, 1934.
50. Willius, F. A.: The Progression of Myocardial Disease as Recorded by Serial Electrocardiograms, M. Clin. North America **16**: 1493, 1933.
51. Willius, F. A., and Anderson, M. J.: Transient Recurrent Complete Bundle Branch Block, Am. Heart J. **10**: 248, 1934.
52. Willius, F. A., and Keith, N. M.: Intermittent Incomplete Bundle Branch Block, Am. Heart J. **2**: 255, 1927.
53. Wolferth, C. C., and Margolies, A.: Asynchronism on Contraction of the Ventricles in the So-called Common Type of Bundle Branch Block: Its Bearing on the Determination of the Side of the Significant Lesion and on the Mechanism of Split First and Second Heart Sounds, Am. Heart J. **10**: 425, 1935.

54. Wolferth, C. C., Wood, F. C., and Bellet, S.: Acute Cardiac Infarction Involving Anterior and Posterior Surfaces of Left Ventricle, Arch. Int. Med. **56**: 77, 1935.
55. Wood, F. C., Jeffers, W. A., and Wolferth, C. C.: Follow-Up Study of 64 Patients With a Right Bundle Branch Conduction Defect, AM. HEART J. **10**: 1056, 1935.
56. Willius, F. A.: Clinical Features of Cases Exhibiting Electrocardiograms Conforming to Those of Experimental Complete Bundle Branch Block, AM. HEART J. **1**: 576, 1926.
57. Lewis, T.: The Spread of the Excitatory Process in the Vertebrate Heart, Phil. Trans. Roy. Soc. **207B**: 221, 1916, Part IV.
58. Lewis, T.: Clinical Electrocardiography, Ed. 3, London, 1924, Shaw & Sons.
59. Wilson, F. N., Macleod, A. G., and Barker, P. S.: The Interpretation of the Initial Deflections of the Ventricular Complex of the Electrocardiogram, AM. HEART J. **6**: 637, 1931.
60. Wilson, F. N., and Herrmann, G. R.: An Experimental Study of Incomplete Bundle Branch Block and of the Refractory Period of the Heart of the Dog, Heart **8**: 229, 1921.
61. Foster, P. C.: The Relation of the Position of the Heart to the Initial Ventricular Deflections in Experimental Bundle Branch Block, AM. HEART J. **10**: 1042, 1935.
62. Katz, L. N., Landt, H., and Bohning, A.: The Delay in the Onset of Ejection of the Left Ventricle in Bundle Branch Block, AM. HEART J. **10**: 681, 1935.
63. Kossmann, C.: The Precordial Electrocardiogram in Myocardial Infarction. Thesis Submitted in Partial Fulfillment of the Requirements for the Degree of Doctor of Medical Science at New York University, April 1, 1938.
64. Kountz, W. B., Prinzmetal, M., and Smith, J. R.: The Effect of Position of the Heart on the Electrocardiogram. II. Observations Upon the Electrocardiogram Obtained From a Dog's Heart Placed in the Human Pericardial Cavity, AM. HEART J. **10**: 614, 1935.
65. Maher, C. C.: Electrocardiography, Baltimore, 1934, William Wood & Company.
66. Saphir, O., Prest, W. S., Hamburger, W. W., and Katz, L. N.: Coronary Arteriosclerosis, Coronary Thrombosis, and the Resulting Myocardial Changes, AM. HEART J. **10**: 567, 1935.
67. Talley, J. E., and Reed, O. K.: A Study of Twenty-Eight Cases of Bundle Branch Block, AM. HEART J. **1**: 262, 1926.
68. Van Nieuwenhuizen, C. L. E., en Matthijssen, E.: Het Electrocardiogram in vier afleidingen bij bundel-en vertakkingsblock, Nederl. tijdschr. v. geneesk. **81**: 5308, 1937.
69. Wenckebach, K. E., and Winterberg, H.: Die unregelmässige Herztätigkeit, Tafelband, Leipzig, 1927, Wilhelm Engelmann.
70. Yater, W. M.: Pathogenesis of Bundle Branch Block, Arch. Int. Med. **62**: 1, 1938.
71. Wilson, F. N., Hill, I. G. W., and Johnston, F. D.: The Form of the Electrocardiogram in Experimental Myocardial Infarction, AM. HEART J. **9**: 596, 1934.
72. Wilson, F. N.: In Diseases of the Coronary Arteries and Cardiac Pain, New York, 1936, The Macmillan Co. Edited by Robert L. Levy.
73. Fahr, G.: An Analysis of the Spread of the Excitation Wave in the Human Ventricle, Arch. Int. Med. **25**: 146, 1920.
74. Wilson, F. N., Johnston, F. D., Cotrim, N., and Rosenbaum, F. F.: Relations Between the Potential Variations of the Ventricular Surface and the Form of the Ventricular Electrocardiogram in Leads From the Precordium and the Extremities, Tr. A. Am. Physicians **56**: 258, 1941.

AURICULAR INFARCTION

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AURICULAR infarction, as a distinct entity, is rarely reported, and the possibility or probability of such an occurrence is hardly even mentioned in textbooks on heart disease. Most discussions of myocardial infarction describe an anterior and posterior type, and dismiss other involvement with the statement that infarction after occlusion of the smaller branches of the coronary arteries is unusual because of the collateral blood supply.

In 1938, Bean[1] reported a series of 287 cases of myocardial infarction, including two definite auricular infarcts and one case of syphilitic infarction of the left ventricle in which there was a small scar in the auricular appendage. At that time, he stated: "It is improbable that the rarity of reported cases of infarct of the auricle is a true indication of its incidence." Also in 1938, Feil, Cushing, and Hardesty[2] reported two instances of auricular infarction in thirty-four cases of myocardial infarction. Langendorf,[3] in 1939, reported a case of infarction of the right auricle, with electrocardiographic changes on the day previous to death which were attributed to the lesion. A comparatively larger number of cases of rupture of the heart have been reported, with not infrequent involvement of the auricle, chiefly the right. Infarction of the auricle is regarded as a common cause of rupture. Recently (1942), Cushing, Feil, Stanton, and Wartman,[4] of Western Reserve University, reported 182 cases of myocardial infarction, including thirty-one, or 17 per cent, in which the auricle was involved. This is the highest incidence reported. However, in only six of these was the auricle alone involved, without infarction of the ventricle.

Most experimental evidence and some of the clinical reports suggest that certain electrocardiographic changes may be indicative of the occurrence of auricular infarction, although these are not constant. Disturbances of the auricular mechanism, such as auricular fibrillation, auricular premature beats, auricular flutter, and wandering pacemaker, are considered by some to be the most reliable evidence. Other reports describe an elevation of the P-Ta segment in Lead I with involvement of the left auricle, and similar changes in the P-Ta segments of Leads II and III with lesions of the right auricle. The P waves may be broadened, inverted, diminished or increased in amplitude, slurred, or notched.

Abramson, Fenichel, and Shookhoff[5] were able to produce constant changes in the electrocardiograms of dogs and cats by cauterization of the auricles. When the anterior or posterior surface of the right auricle was injured, the P-Ta segment of Lead I showed a depression, where-

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as similar damage to the left auricle resulted in an elevation of this segment. The P-Ta segments of Leads II and III were depressed with cauterization of either right or left auricle, and therefore did not aid in localizing the lesion. Of their observations, these investigators said: "The constancy with which P-Ta segment changes in the dog and cat followed the production of auricular damage leads one to believe that possibly close examination of the comparable portion of the human electrocardiogram might be of value in those instances in which the rare clinical condition of auricular infarction with rupture is suspected."

Although auricular infarction with rupture may be rare, auricular infarction without rupture is apparently a more common occurrence than was formerly supposed, and it is not unreasonable to expect that similar electrocardiographic changes might occur with infarction which did not result in rupture. The observation has been made that these changes may be obscured in some instances by the beginning of ventricular activity (QRS).

Depression or elevation of the P-Ta segments may occur in normal electrocardiograms. However, in a series of 200 normal electrocardiograms[6] in which depression of this segment occurred in Lead I in 55 per cent, it did not exceed 0.8 mm. in any case. Only two records showed an elevation of P-Ta, and in neither of these was it more than 0.4 mm. In another series of 100 normals,[7] elevation of the P-Ta segment was found only twelve times in Lead III and not at all in Leads I or II. Depression was more common; it occurred fourteen times in Lead I, fifty-four times in Lead II, and twenty-one times in Lead III. The maximum deviation in either direction was 0.5 mm. It seems highly probable, therefore, that any electrocardiogram in which the P-Ta segment is depressed (deviates from the normal level) more than 0.8 mm. or elevated more than 0.5 mm. may be considered strongly suggestive of auricular damage, particularly if the changes occur in Lead I.

Because of the dearth of reports of auricular infarction, and also because of the lack of definite diagnostic clinical signs, it was thought of value to report the following cases.* Three of these patients had true auricular infarcts, and the fourth was thought to have auricular infarction because of suggestive electrocardiographic changes, and is included for that reason.

REPORT OF CASES

The first case was that of a man, 36 years of age, who complained of several attacks of substernal pain (under the lower half of the sternum), radiating outward and downward and into both arms below the elbows. Physical examination was entirely negative on two occasions, and an attempt to reproduce the pain by extreme exertion was unsuccessful. An electrocardiogram, taken four months after the first attack, did not show any suggestive variations from the normal. Five days after the electrocardiogram was taken, the patient apparently had an attack of severe pain, associated with vomiting, and died in about thirty minutes.

*These cases were observed in the past year and a half at the Presbyterian Hospital of Pittsburgh.

Autopsy revealed a dark-red, sharply circumscribed, hemorrhagic lesion of the wall of the right auricle (Fig. 1). This area was roughly circular, and measured approximately 1 cm. in diameter. Incision into this area showed that it was a true infarct; the wall at this point was a very dark red as a result of intramural hemorrhage. This lesion was located at, or very near, the auriculoventricular node, just below the opening of the inferior vena cava and to the right of the opening of the coronary sinus. There were no old scars or other lesions. The coronary arteries and their branches showed irregularly distributed sclerosis, and, in some places, were quite hard and almost occluded. This was especially marked in the main vessels.

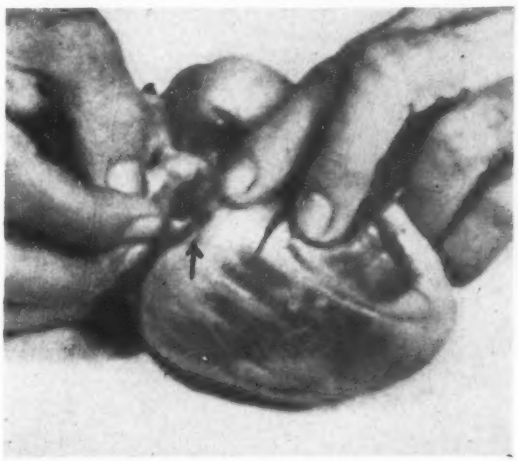

Fig. 1.

The second case was that of a woman, 58 years old, who was admitted to the hospital with a history of sudden onset of severe dyspnea, with little or no pain. Signs of circulatory failure were evident in the poor quality of the heart sounds, rapid pulse rate, marked cyanosis, moist râles at the bases of both lungs, and slight peripheral edema. The diagnosis on admission was coronary occlusion. An electrocardiogram (Fig. 2), taken the following day, showed inversion of the P waves in Leads II and III, depression of the P-Ta segments in Lead I, and elevation of the corresponding portions in Leads II and III. There was a peculiar, dome-shaped appearance of the P-Q segments in Lead III which might be considered the equivalent of the RS-T changes which are characteristic of ventricular lesions. Because of these changes, involvement of the auricle, presumably the right, by infarction was suggested. The patient died forty-four hours after admission, and autopsy revealed dilatation of the right auricle and a rim of dark discoloration along the A-V junction, extending into the auricular appendage (Fig. 3). On cut section the wall here was infiltrated with blood. There was moderate atheroma of the aorta and coronary vessels, but no occlusion of the large branches. The auricular lesion was reported as due to occlusion of a small vessel in the infarcted area. The right ventricle, left auricle, and left ventricle showed no areas of infarction.

In February, 1943, a woman, 26 years of age, was admitted to the hospital with a provisional diagnosis of congestive failure probably due to rheumatic heart disease, although definite evidence of a valvular lesion

was not present. Profuse sweating, marked pallor, and moderate dyspnea were present. Examination of the heart showed that it was enlarged to the left; the heart action was irregular, and apparently there were long periods of coupling. The sounds were accentuated at the apex, and, at times, a low, rumbling sound suggestive of a murmur was heard

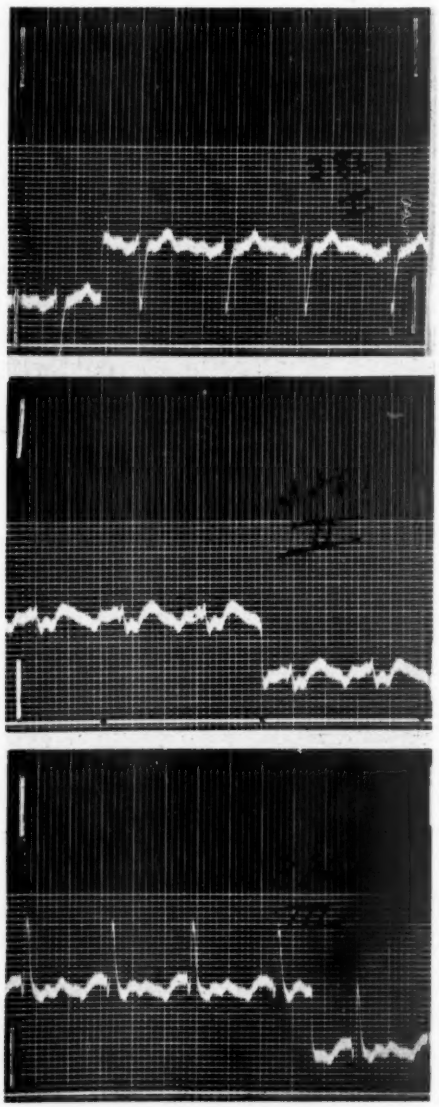

Fig. 2.—See text.

just at the beginning of diastole. A teleoroentgenogram showed extreme enlargement of the heart with contours suggestive of mitral stenosis. An electrocardiogram (Fig. 4), taken the day after admission, revealed what was apparently 2:1 A-V heart block; alternate P waves were fused with T waves. The P waves were slightly notched in Lead I and peaked in

Leads II and III. Because of large, broad complexes in the usual position of the T waves, it was difficult to ascertain exact deviations from the base line. The P-Ta segments of Leads II and III seemed to be slightly depressed. No adequate explanation could be offered for the unusual changes, but the possibility of coronary thrombosis with unusual effects on the myocardium and conductive mechanism was suggested. Three days after admission, the patient died, and examination of the heart post mortem showed an infarct, about 2 by 3 cm., in the wall of the right auricular appendage. The right auricle was markedly dilated. A large ulceration was found on the interventricular septum below the tricuspid valve, extending through the wall into an aneurysmal sac. Section through the auricular area showed a true infarct. The final diagnosis was acute ulcerative endocarditis and infarction of the right auricular appendage.

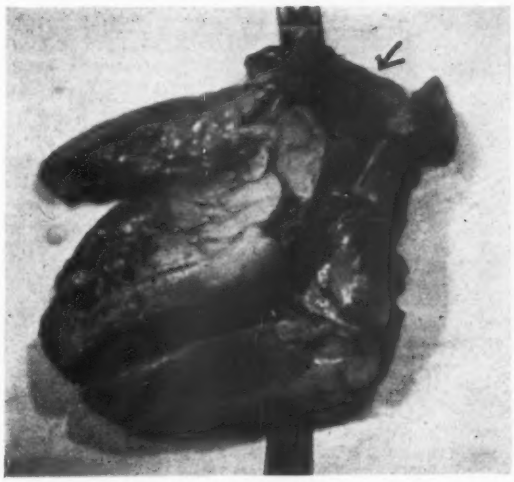

Fig. 3.

A white man, 59 years of age, was admitted to the hospital April 5, 1943, with the complaint of severe pain in the jaw, neck, chest, and abdomen which began suddenly while doing light work. The pain was constant, not relieved by rest, and there had been no previous attacks. Physical examination revealed slight pallor, a cold, clammy skin, dyspnea, and moderate cyanosis. There was a systolic murmur at the apex, and also a sound which was interpreted as a pericardial friction rub. The heart rate was 72 per minute, and the blood pressure, 178/110. A tentative diagnosis of coronary occlusion was made, and electrocardiograms (Fig. 5) seemed to confirm this diagnosis. Changes considered suggestive of auricular damage were present, as shown by the broadened, dome-shaped P waves in Lead I, notched, W-type P waves in Leads II and III, and the depressed P-Ta segments of Lead III. These abnormalities were fairly constant in all the tracings taken, but there were some variations, suggesting repair of the lesion, eight days after the onset. Because of the failure of the blood pressure to fall after the initial attack, and also because the pain, as described, was not typically that of coronary occlusion, the diagnosis was considered as only tentative. The pain continued in moderate severity until April 24, when death

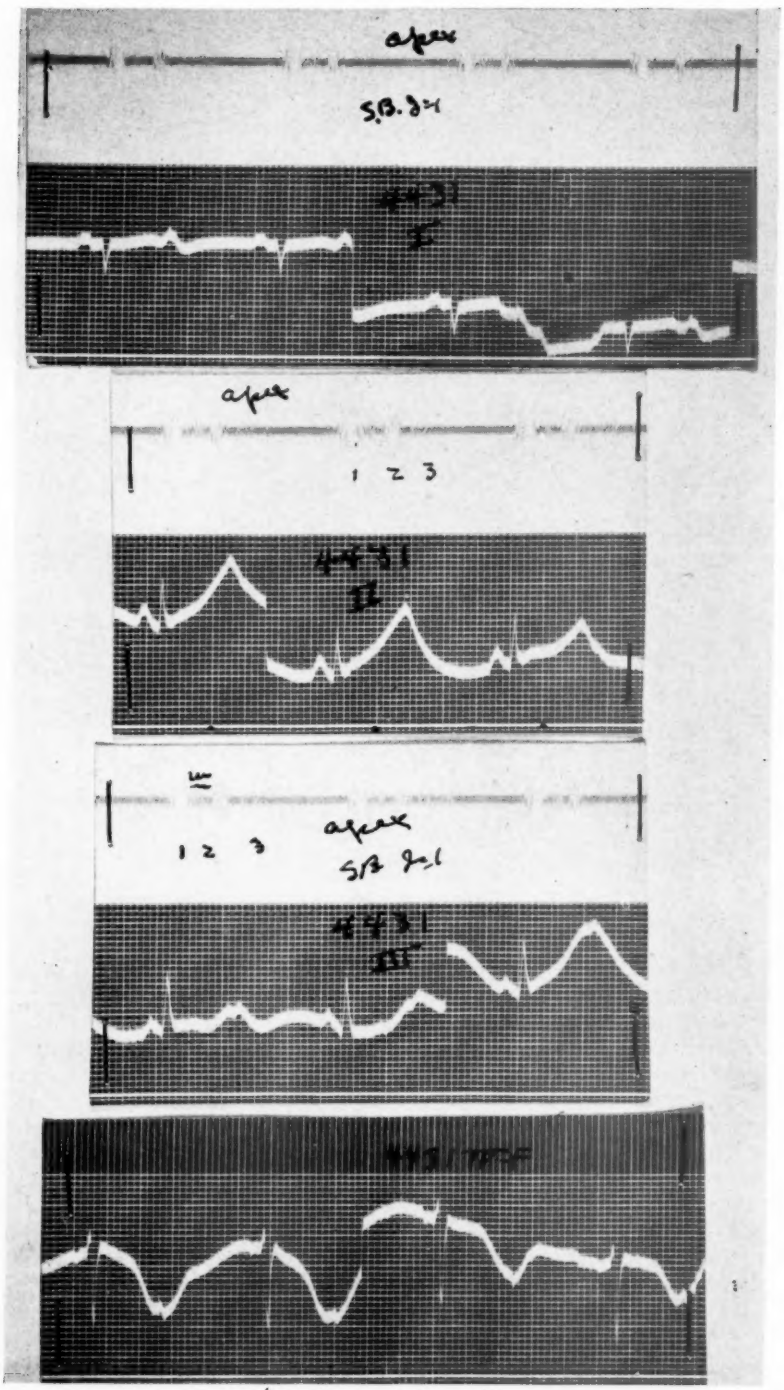

Fig. 4.—Right axis deviation. Large, broad complexes in Leads II, III, and IVF in position of T waves. Sound: variable third heart sound. Vibrations of faint systolic murmur.

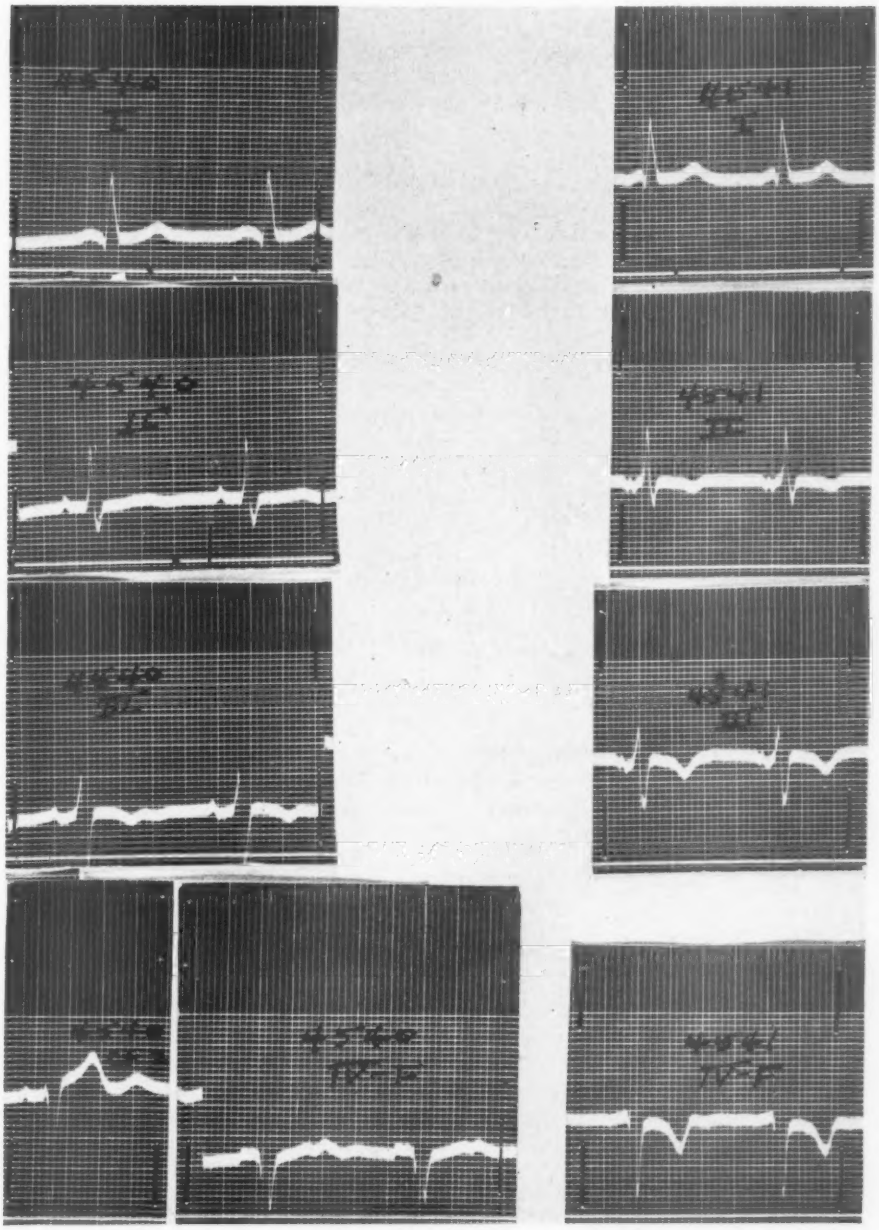

Fig. 5.—April 5, 1943, five and one-half hours after acute pain in left side of jaw, neck, and precordium. P waves flattened in Leads I and IVF. Ventricular complexes show well-developed left axis deviation and moderate slurring. Small Q waves in Leads I, IVF, and CF_5; T waves up in Lead I, diphasic in Lead II, inverted in Lead III, up in Leads CF_2 and CF_5, and diphasic in Leads CF_5 and IVF.

April 6, 1943, twenty-seven and one-half hours after attack. P smaller in Lead I, split in Leads II and III. P-Ta depressed in Lead III. T waves negative in all leads.

occurred suddenly. On post-mortem examination of the chest, the left pleural space was found to be filled with blood and clots, compressing the left lung upward so that it occupied only one-fifth of its usual space. The pericardium was adherent to the lateral chest wall, but the cavity was dry when opened. The heart, aorta, and mediastinal structures were removed en masse, and the source of the bleeding was found to be rupture of a false aneurysmal sac at the level of the fifth thoracic vertebra. At the level of the origin of the left subclavian artery, there was a tear in the aorta at a thinned-out area, at which point the surrounding connective tissue was thickened and adherent. Distally along the course of the aortic arch and the beginning of the descending aorta, thickened mediastinal pleura formed a false aneurysm which was partially filled with thrombus, the rupture of which had produced the fatal hemorrhage. Sclerotic patches were present on the intima, and interstitial hemorrhage extended proximally along the arch and *involved the auricles,* particularly the right. The left ventricle was thickened and somewhat dilated. The auricles were dilated. There were small calcified areas on the valve cusps, and an old, healed vegetation was seen on one cusp of the mitral valve. The coronary openings were patent, and the coronary arteries were sclerotic and tortuous, but no evidence of myocardial infarction was seen. No auricular infarct was found in this case; however, the hemorrhage into the auricles may have produced sufficient damage to cause the changes noted in the P-Ta segments of this patient's tracings.

SUMMARY

Three cases of distinct auricular infarction, without ventricular involvement, are presented. A fourth case in which the electrocardiograms showed changes apparently typical of auricular damage proved to be one of ruptured, false aneurysm, with hemorrhagic infiltration of the auricles.

The first case was interesting because of the unfortunate location of the small infarct; it might have been less serious if it had been located in the ventricle.

In three of the four cases there were deviations of the P-Ta segments conforming to that described as typical of auricular damage. In one there was also an apparent disturbance of the A-V conduction pathway; this was most likely due to the ulceration through the interventricular wall.

All of the infarcts were located in the right auricle.

REFERENCES

1. Bean, W. B.: Infarction of the Heart, Ann. Int. Med. **12**: 71, 1938.
2. Feil, H., Cushing, E. H., and Hardesty, J. T.: Accuracy in Diagnosis and Localization of Myocardial Infarction, AM. HEART J. **15**: 721, 1938.
3. Langendorf, R.: The Electrocardiogram of Auricular Infarction, Acta med. Scandinav. **100**: 136, 1939.
4. Cushing, E. H., Feil, H., Stanton, E. J., and Wartman, W. B.: Infarction of the Cardiac Auricles, Brit. Heart J. **4**: 17, 1942.
5. Abramson, D. I., Fenichel, N. M., and Shookhoff, Chas.: A Study of Electrical Activity in the Auricles, AM. HEART J. **15**: 471, 1938.
6. Shipley, R. A., and Hallofan, W. R.: The Four Lead Electrocardiogram in Two Hundred Normal Men and Women, AM. HEART J. **11**: 325, 1936.
7. Larsen, K., and Skulason, T.: The Normal Electrocardiogram, AM. HEART J. **22**: 625, 1941.

THE EFFECT OF CHRONIC LEAD POISONING ON ARTERIAL BLOOD PRESSURE IN RATS

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RECENTLY, Fouts and Page[1] reported their inability to produce arterial hypertension in one dog which was chronically poisoned with lead over a period of three years. A second dog, poisoned for a much shorter time, likewise failed to develop hypertension. They state that "the belief that chronic lead poisoning leads to arterial hypertension extends deep into the annals of clinical medicine, but the evidence on which it is based is unconvincing," and conclude from their negative results that "the problem in human beings needs reinvestigation."

Although conclusions from studies on animals cannot always be carried over to man, it would certainly seem that lead would be an unlikely cause of hypertension in man if it could not produce hypertension in an animal, especially in an animal which is known to be capable of developing hypertension from some other cause. Therefore, it seemed well to repeat the study with a different species of animal.

METHOD

Healthy albino rats, weighing 150 to 200 grams, were used. Fifteen were successfully carried through the experimental procedure. Lead acetate was given in a dose of 90 mg. daily, omitting every seventh day throughout the experimental period. This corresponds to about 70 mg. of lead, as such, per day, and was given dissolved in 2 c.c. of water by stomach tube.

The blood pressure was measured by the indirect method described by Griffith,[2] and, in two animals, directly by inserting a needle into the abdominal aorta. This needle was connected by a rubber tube, filled with saline, to a mercury manometer, the inertia of which was so great that there was no visible pulsation in the mercury column. Under such circumstances, the pressure measured is mean pressure, in contrast with the indirect method, which is thought to measure systolic pressure. Hereafter, the term "blood pressure," when unqualified, will indicate blood pressure measured by the indirect method.

In ten of the fifteen animals, the blood pressure was measured before beginning the administration of lead, and found to be normal. In the remaining five animals, the blood pressure was first measured ten days after beginning the administration of lead, and found to be normal at that time. It was therefore assumed that it had been normal initially. Thereafter, the blood pressure was measured every fifteen to twenty days, depending upon convenience. More frequent readings were considered impractical because each necessitated induction of surgical anesthesia with ether. The blood pressure was measured four times in four

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animals, three times in seven animals, and twice in three animals. All animals charted survived at least until the thirtieth day, after which, some were sacrificed for acute experiments and some died; four animals survived until the experiment was terminated on the eightieth day.

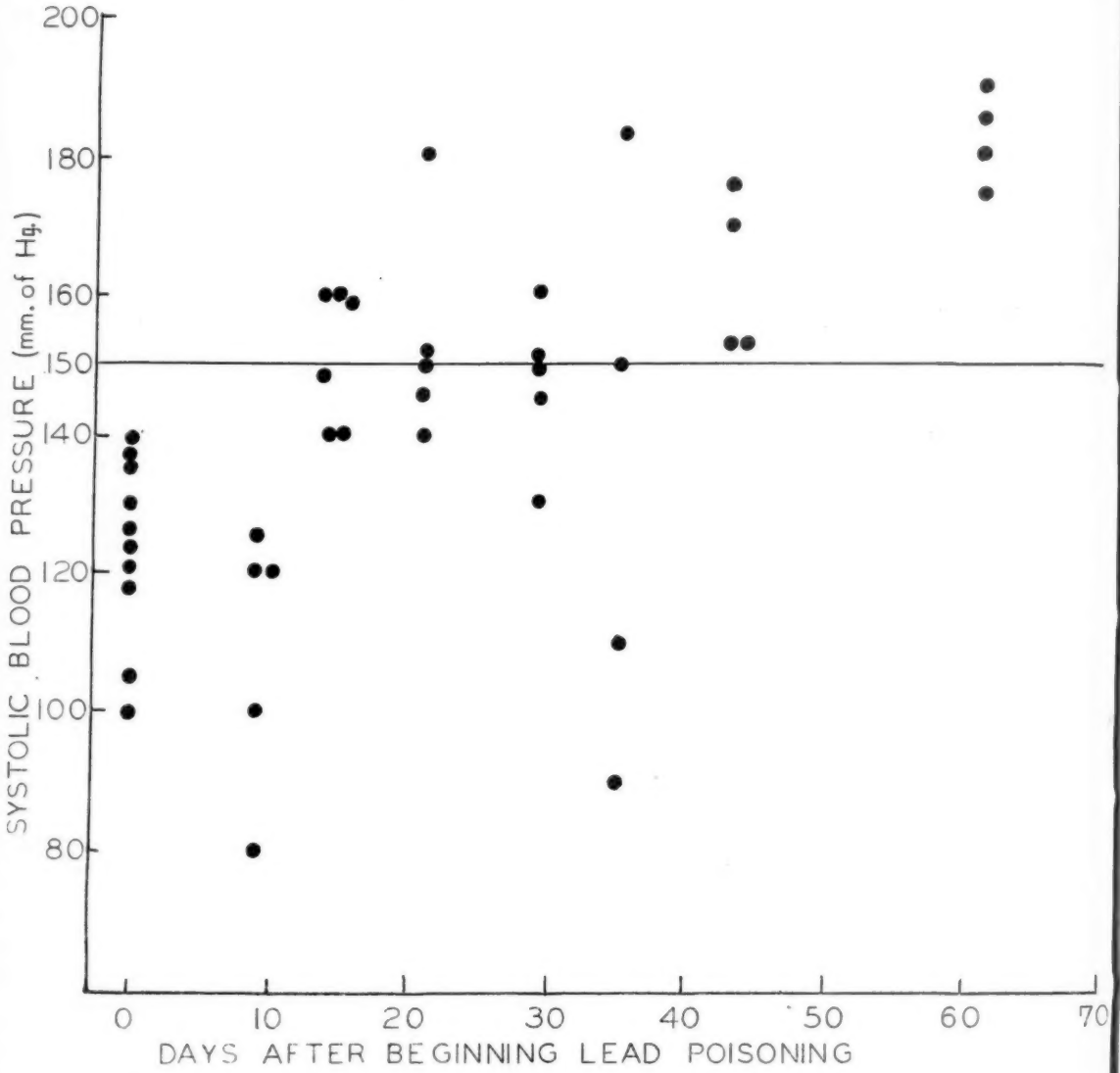

Fig. 1.—Chart showing the effect of chronic lead poisoning on the systolic blood pressure of fifteen rats.

RESULTS

The results are shown in Fig. 1, in which only the indirect measurements are charted. The horizontal line at 150 mm. represents the upper limit of normal by this method. It is apparent that all animals that survived forty days were hypertensive.

The mean blood pressure, measured directly by a needle in the aorta, normally does not exceed 90 mm. of mercury. In two hypertensive animals in which the blood pressure was measured by both methods, the results were as follows:

Rat 1.—Indirect (systolic) blood pressure, 180 mm. of mercury; direct (mean) blood pressure, 119 mm. of mercury.

Rat 2.—Indirect (systolic) blood pressure, 160 mm. of mercury; direct (mean) blood pressure, 122 mm. of mercury.

CONCLUSION

Chronic lead poisoning can produce arterial hypertension in rats.

REFERENCES

1. Fouts, P. J., and Page, I. H.: The Effect of Chronic Lead Poisoning on Arterial Blood Pressure in Dogs, AM. HEART J. **24**: 329, 1942.
2. Griffith, J. Q., Jr.: Indirect Method for Determining Blood Pressure in Small Animals, Proc. Soc. Exper. Biol. & Med. **32**: 394, 1934.

AN ELECTROCARDIOGRAPHIC AND CLINICAL STUDY OF VARIOUS SO-CALLED CARDIAC DRUGS

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FOR years, many pure glycosides have been in common use in the treatment of congestive heart failure. Many of these have been given parenterally in the hope of facilitating rapid digitalis action.[1] Until recently, there has been little in the literature to prove that they act rapidly, and their use in the past has been based entirely on the claims of their various manufacturers. In a previous communication, one of us[2] observed the rapid effect of one of these glycosides on the electrocardiograms of two normal control subjects at ten-minute intervals for a period of two hours or more, and subsequently noted the effect of this glycoside at frequent intervals in many cases of congestive heart failure. The electrocardiographic changes appeared to follow a characteristic form in all subjects under observation. This led us to believe that some electrocardiographic change might typify each of the various glycosides, and that these changes might be characteristic of specific drug action on the myocardium. Since this initial observation, we have noted varying electrocardiographic changes after the use of many glycosides, and we believe that this warrants further study.

The effects of various digitalis bodies on the electrocardiogram of man and animal have been recorded frequently.[3-6] Most of these studies were mainly concerned with general changes in the polarity of the T wave. No attempt was made to evaluate the changes in the RS-T segment and T wave quantitatively and individually for each preparation used. Other studies failed to record characteristic digitalis effect because of failure to evaluate the action of the drug in the various electrocardiographic leads. McMillan and Bellet[7] called attention to various changes in the S-T segment and other electrocardiographic components after the administration of digitalis which they felt were quite characteristic. Our observations lead us to believe that, if all of the above factors be taken into consideration, the electrocardiographic criteria of a digitalis effect are quite dependable. Furthermore, we have been led to believe that many digitalis glycosides[8] vary in their effect on the electrocardiogram.

Changes in the RS-T segment and T waves are not entirely limited to the action of digitalis. It is generally accepted that many physiologic and pathologic changes in the myocardium alter these constitu-

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ents. Coronary anoxemia,[9] hyperventilation,[10] and innumerable changes in cardiac function are known to produce both segment changes and alteration in the polarity of the T waves. Master, Friedman, and Dack[11] have shown that, after exercise, a general depression of the RS-T segment and T waves may occur in the presence of coronary insufficiency. This study suggests that digitalis depression of these electrocardiographic components may be the result of cardiac anoxia. Digitalis effects on the electrocardiographic constituents have been variously described by Oettel,[12] Gold and his co-workers,[13] and others.[14-18] Wegria and his associates,[19] in a recent study, felt that changes in the electrocardiogram after digitalis administration appeared to be characteristic for each type of preparation used.

The use of the electrocardiogram for clinical standardization of digitalis preparations has been suggested by many clinicians. These observations have been discounted in the past, and we are led to believe that a more detailed study, embracing all phases of electrocardiographic change caused by various digitalis preparations, may lead to a more consistent series of observations. Although our observations are preliminary, we feel that they support this contention.

TABLE I

DRUG USED	DOSAGE ADMINISTERED	METHOD OF ADMINISTRATION
Digifolin (Ciba)	4 c.c., 2 cat units	Intravenously
Digalen (Roche)	4 c.c., 2 cat units	Intravenously
Digilanid (Sandoz)	8 c.c., 4.8 cat units	Intravenously
Ouabain (Smith)	4 c.c., 10 cat units	Intravenously
Cedilanid (Sandoz)	8 c.c., 1.6 mg.	Intravenously
Digoxin (B. W. & Co.)	3 c.c., 3 cat units	Intravenously
Scillaren-B (Sandoz)	1 c.c., 1 cat unit	Intravenously
Strophosid (Sandoz)	2 c.c., 1 mg.	Intravenously
Strophanthin-K (Abbott)	2 c.c., 0.5 mg.	Intravenously
Coramine (Ciba)	1.5 c.c. (Pyridine beta-carboxylic acid diethylamide of nicotinic acid)	Intravenously
Metrazol (Schering)	1 c.c. (1½ grains of pentamethylenetetrazol)	Subcutaneously

The drugs listed in Table I were given in the dosage recommended by the manufacturer. All preparations, with the exception of metrazol, were given rapidly by the intravenous method. In the case of digoxin, the recommended dose was diluted with physiologic saline to make a total volume of 10 c.c.

METHOD OF STUDY

Each preparation was given to two subjects who were free from cardiovascular disease. Normal renal function was a prerequisite in each case. Investigation was made to ascertain whether or not the subjects had drug idiosyncrasies. Prior to the study, an electrocardiogram was recorded in the four conventional leads recommended by the American Heart Association. A Sanborn Cardiette and a portable Cambridge machine were used alternately, and were so standardized that a 1 cm. deflection represented a potential difference of 1 mv. Each subject was

placed in a supine position, where he remained until the completion of the study. After the administration of each drug, Lead II was recorded at ten-minute intervals for a period of not less than two hours. When no electrocardiographic change was noted after one hour's observation, the study was discontinued. Throughout the period of observation, each subject was examined from time to time, and interrogated relative to the appearance of untoward symptoms.

RESULTS OF STUDY

1. *Cedilanid (Lanatoside C).*—The average heart rate of the two subjects that received 1.6 mg. of Lanatoside C was 90 per minute at the commencement of the experiment. An appreciable reduction of this rate was not noted until two hours after the administration of the drug, and this reduction was only 5 beats per minute. One subject had frequent ventricular ectopic beats before the drugs was given, and these disappeared completely throughout the period of observation. In both subjects, a gradual depression of the RS-T segment was noted, beginning 10 minutes after the drug was administered and continuing for a period of from 90 to 100 minutes. At this time, the RS-T depression reached its maximum of 2 mm. A return of this depression was first noted 110 minutes after the drug was given, and a gradual return of this segment to normal occurred in approximately twenty-four hours. The positive polarity of the T waves in both subjects diminished, and could be considered isoelectric 80 minutes after the drug was given. The T waves remained in this isoelectric state throughout the entire period of observation, and, at the end of twenty-four hours, their former positive polarity was still mainly lacking. Neither subject presented untoward symptoms or physical signs attributable to Lanatoside C.

2. *Ouabain.*—One subject received 10 cat units of ouabain which was recommended as active, although its potency expiration date had almost arrived. This preparation was found to be ineffective, clinically and electrocardiographically. The remaining subject received fresh ouabain solution directly from the manufacturer. The effect of the drug was almost immediate on both the heart rate and the electrocardiogram. At the end of 130 minutes of observation, the heart rate was reduced from 92 per minute to 52 per minute. This marked sinus effect continued for four hours after the completion of the experiment. The maximum depression of the RS-T segment was noted ten minutes after the drug was given. The T wave also showed its maximum depression within ten minutes. The quantitative depression of the RS-T segment and the T wave approximated more than 1 mm. at this time. Both of these components gradually increased their positive polarity, and, at the end of 120 minutes, two-thirds of their depression had been nullified. This rapidity of action on the electrocardiogram was unlike any of the other glycosides used in this study. It possibly accounts for the sudden deaths which we have observed when it has been given to patients with congestive heart failure who had been receiving digitalis previous to its administration

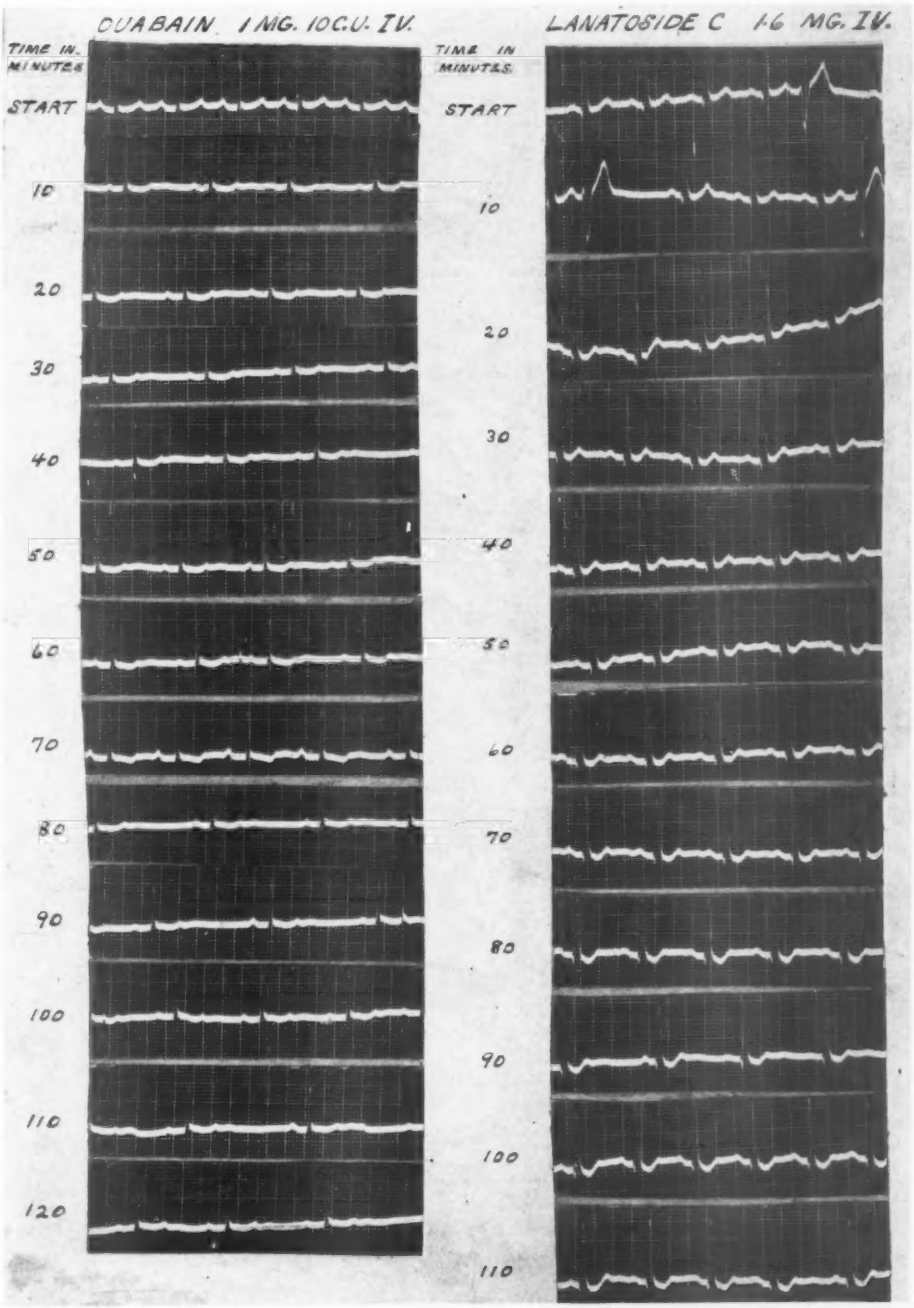

Fig. 1.—Comparative serial electrocardiograms recorded in Lead II. (Note rapid change with ouabain and gradual change with Lanatoside C on RS-T segment and T wave.)

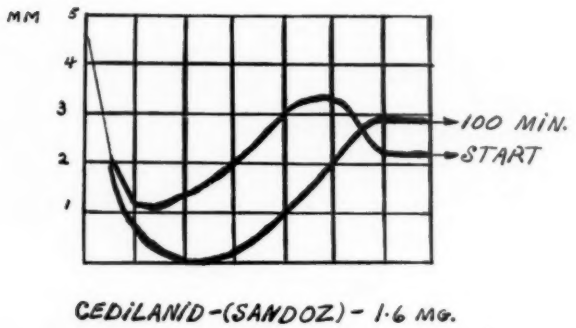

Fig. 2.—Maximum cedilanid deflection. 1 cm. ≡ 1 mm. on electrocardiogram.
***Diagrammatic Scheme.*—Changes in the electrocardiographic pattern of the RS-T segment and T wave before and after* the intravenous† administration of the various cardiac glycosides.**

Scale 1 cm. equals 1 mm. on actual tracings.

***In the case of ouabain, a return of the pattern to normal is noted.**

†Metrazol was given subcutaneously.

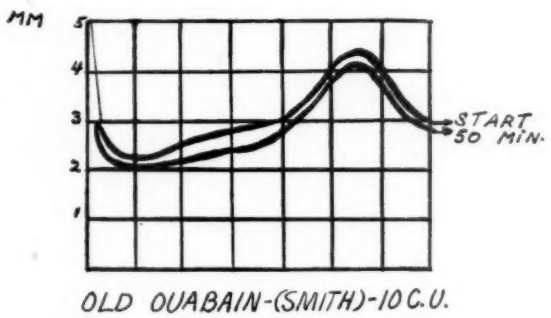

Fig. 3.—Inert ouabain (old). Maximum effect. 1 cm. = 1 mm. on the electrocardiogram.

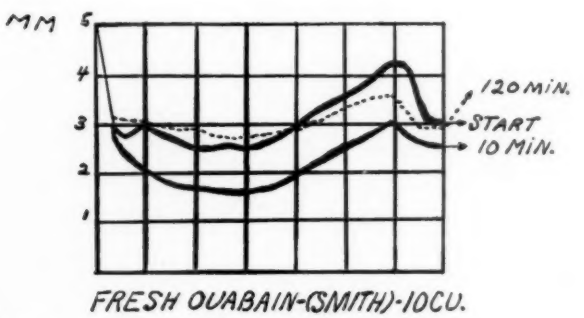

Fig. 4.—Fresh ouabain. Maximum deflection in ten minutes. Dotted line represents return to normal in two hours.

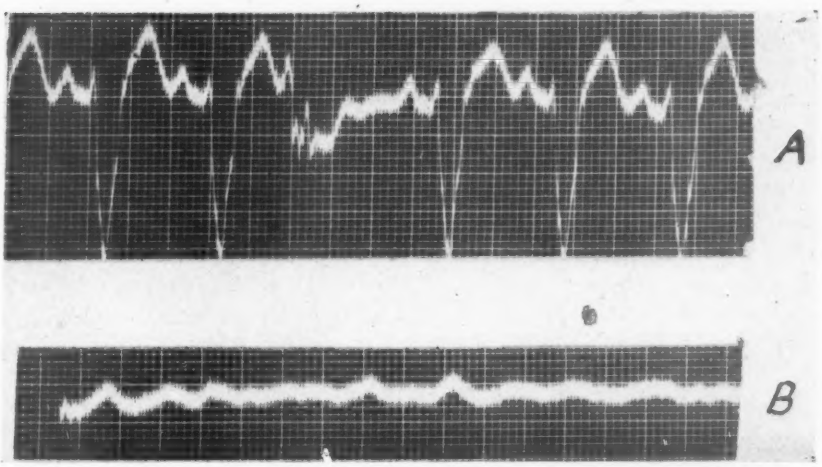

Fig. 5.—F. H., female, age 68 years. Admitted Apr. 12, 1943, with diagnosis of hypertensive heart disease and congestive failure. Electrocardiogram recorded in Lead III demonstrates bundle branch block and ventricular premature contractions. *A*, Ouabain was given intravenously, prior to history of maintenance digitalis therapy. *B*, Within sixty seconds ventricular fibrillation and death resulted.

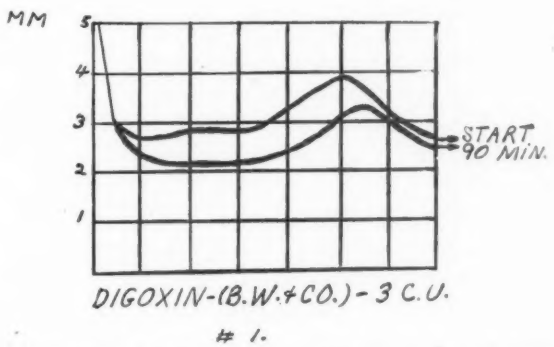

Fig. 6.—Maximum digoxin effect. 1 cm. = 1 mm. on the electrocardiogram.

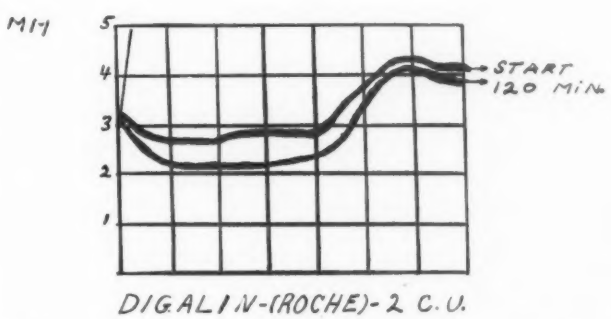

Fig. 7.—Digalen. 1 cm. = 1 mm. on the electrocardiogram.

(see accompanying electrocardiogram of F. H.). There was no evidence of an ouabain effect electrocardiographically, eight hours after the drug was administered.

3. *Digoxin.*—After the intravenous administration of 3 cat units of this drug, gradual depression of the RS-T segment was noted in both subjects. This depression reached its maximum in 120 minutes, and measured ¾ mm. The T wave was gradually depressed in a like manner, and, at the end of 120 minutes, was lowered ½ mm. The action of this drug on the electrocardiogram was not unlike cedilanid, but the degree of depression was far less. As in the case of cedilanid, digoxin produced an almost negligible early sinus effect. The maximum reduction in heart rate throughout the entire 120-minute period of observation was six beats per minute. Evidence of digoxin effect was still apparent eight hours after the completion of the study. No untoward symptomatic or physical effects were noted in either subject throughout the entire course of the study.

4. *Digalen.*—Although the RS-T segment and T wave were depressed only ½ mm. in each subject, a moderate sinus effect occurred in both throughout the 120-minute period of observation. The average reduction in heart rate was 10 beats per minute. This reduction was first noticed 30 minutes after the drug was administered, and continued throughout the 120-minute period of observation. Eight hours after the study, the sinus reduction no longer obtained, but the ½ mm. of RS-T segment and T-wave depression was still apparent. No untoward symptomatic or physical changes attributable to this drug were noted throughout the entire period of study.

5. *Digilanid.*—After the intravenous administration of this drug (4.8 cat units), a gradual reduction in heart rate was noted; this continued for the entire 130 minutes of observation, and averaged 14 beats per minute. A slight sagging effect on the RS-T segment occurred in 20 minutes, and this continued for 70 minutes after the drug was administered, at which time it reached its maximum depression of ⅓ mm. The depression of the T wave occurred gradually after the drug was administered, and, at the end of 130 minutes, the depression reached its maximum of 1½ mm. On a previous study, 2 cat units of this drug were administered to a subject, and the only noticeable effect on the electrocardiogram was a ⅛ mm. depression of the descending limb of the T wave. No untoward symptoms resulted from the administration of this drug.

6. *Strophanthin-K* (Abbott).—One mg. of this drug was given intravenously to two subjects without producing untoward symptoms or physical signs. Throughout the entire experiment, which was conducted for a period of two hours, little or no effect was noted on the RS-T segment and T wave. In one subject there was a slight, questionable depression at the commencement of the RS-T segment. The sinus effect on the heart rate was negligible.

7. *Strophosid* (Sandoz).—Each of two subjects received one mg. of this drug intravenously without untoward clinical effects. Changes in the RS-T segment throughout the entire study were negligible. The only effect on the T wave was a ½ mm. depression of its descending limb. No sinus effect was noted.

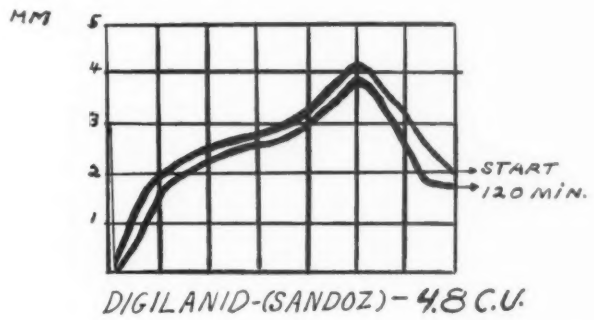

Fig. 8.—Digilanid, maximum deflection. 1 cm. = 1 mm. on the electrocardiogram.

Fig. 9.—Strophanthin-K. Maximum deflection. 1 cm. = 1 mm. on the electrocardiogram.

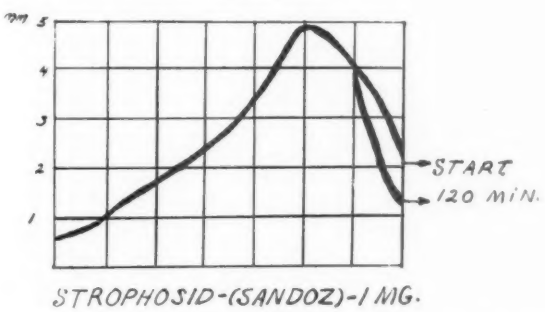

Fig. 10.—Strophosid. Maximum deflection. 1 cm. = 1 mm. on the electrocardiogram.

8. *Scillaren-B.*—Two subjects received 0.144 mg. of this drug without untoward clinical effects. No change in the RS-T segment occurred throughout the entire period of observation. Very slight depression of the descending limb of the T wave was noted 80 minutes after the drug

was given. A slight sinus reduction in heart rate occurred within 10 minutes after the drug was administered, and continued throughout the entire period of observation.

9. *Metrazol.*—This drug was given subcutaneously to two subjects in 2 c.c. doses (3 grains). Approximately 20 minutes after the drug was given, an increase in the depth of respiration was observed. No other clinical change occurred. The RS-T segment, 20 minutes after the drug was given, revealed slight depression (1 mm.), and this depression continued for approximately 60 minutes. This segment change disappeared at thhe end of two hours. Forty minutes after the administration of this drug, a very slight increase in the positive polarity of the T wave was observed (⅓ mm.). This slight increase in positive polarity continued throughout the entire period of observation. An appreciable sinus reduction in the heart rate of approximately 25 beats per minute was noted at the end of two hours.

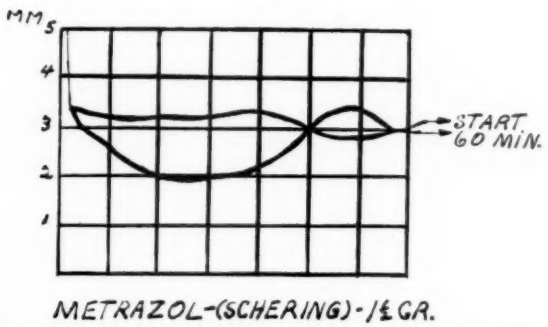

Fig. 11.—Metrazol (given subcutaneously). Maximum effect of 1½ grains. 1 cm. = 1 mm. on the electrocardiogram.

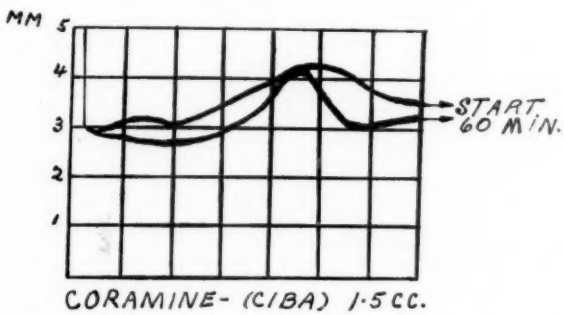

Fig. 12.—Coramine. Maximum deflection. 1 cm. = 1 mm. on the electrocardiogram.

10. *Coramine.*—Three c.c. of this drug were given to two subjects without noticeable clinical effect. The only electrocardiographic change appeared to be slight shortening of the QT interval. A questionable $\frac{1}{10}$ mm. sagging of the RS-T segment was observed in one subject. No sinus effect was noted.

DISCUSSION

Of the various glycosides administered to normal subjects in this study, only three, cedilanid, digoxin, and ouabain, produced significant electrocardiographic change within the two-hour serial study. It is interesting that cedilanid and digoxin act in a similar manner by producing gradual depression of the RS-T segment and T wave, although the former did so more significantly. These drugs are similar in chemical make-up. Digoxin is known to be a degradation product of cedilanid. In the case

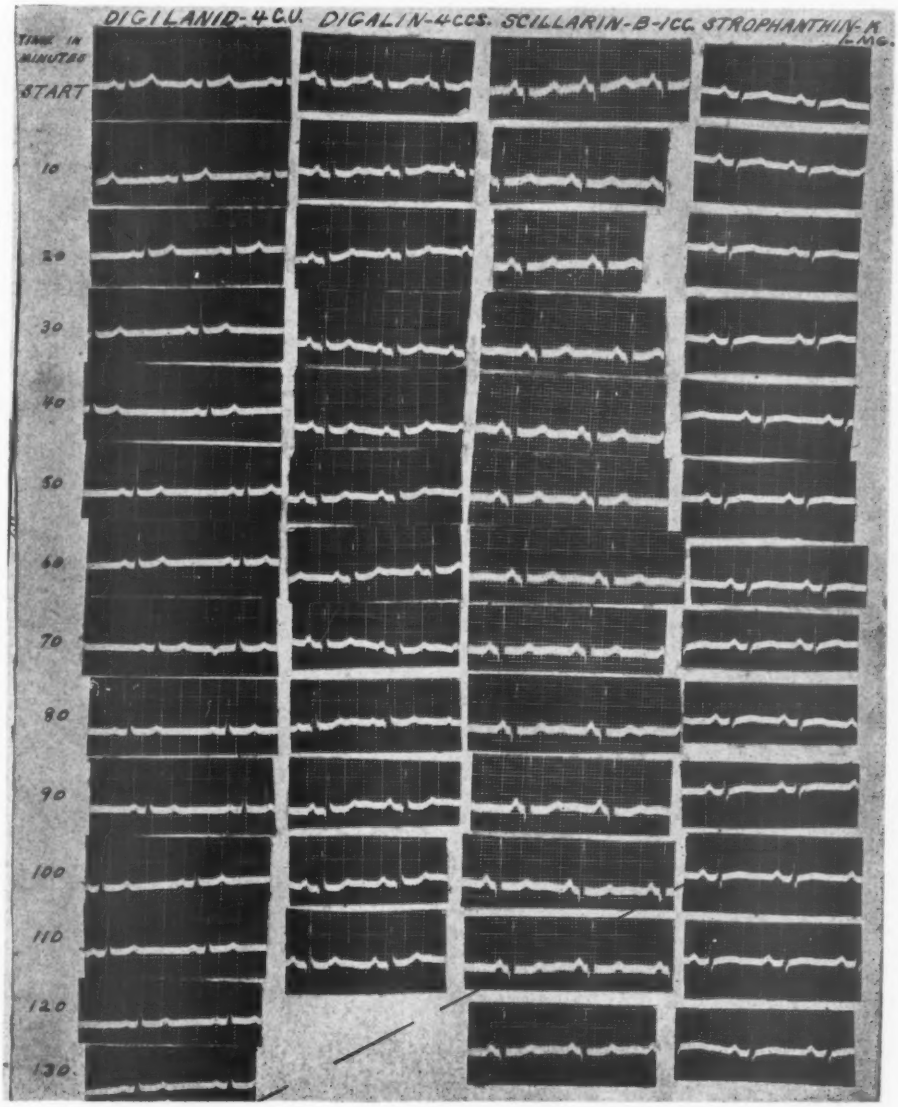

Fig. 13.—Representative serial electrocardiograms, recorded in Lead II following intravenous drugs. (Note sinus effect.)

of active ouabain, the maximum effect on the RS-T segment and T wave occurred within ten minutes after the intravenous administration of the drug. This rapidity of action may in some way be related to the toxic effects occasionally noted when it is given to patients who are already fully digitalized. The return of the electrocardiographic components toward normal seems to follow, inversely, the pattern of electrocardiographic effect. The ouabain effect on the electrocardiogram was two-thirds nullified at the end of the two-hour period of observation, whereas the effects of both cedilanid and digoxin remained almost at a

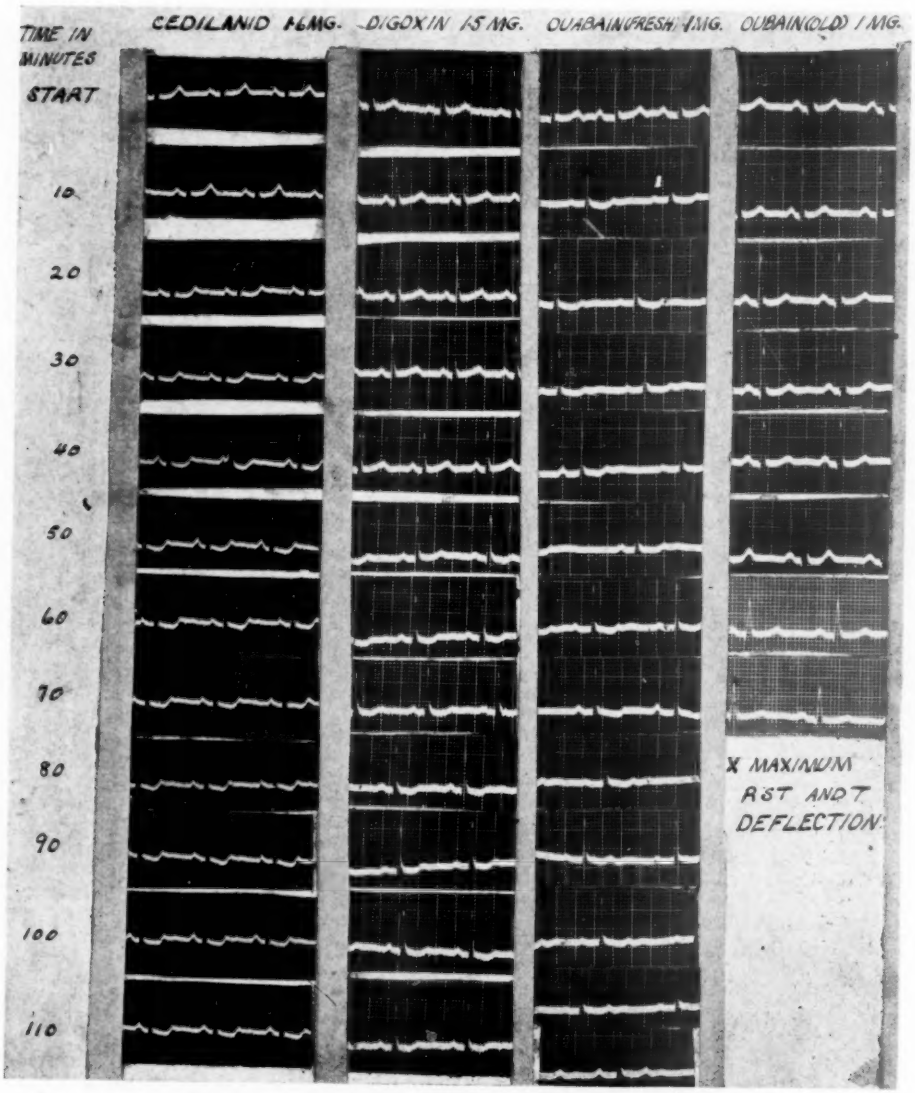

Fig. 14.—Representative serial electrocardiograms using the various glycosides. Recorded in Lead II. Full digitalizing dosage was given intravenously.

maximum until the study was completed. Of these three drugs, ouabain produced the most significant sinus effect. Digalen and digilanid had little electrocardiographic effect. It is quite likely that, had this study been extended, significant changes would have occurred. Both Strophanthus glycosides used in this study failed to produce appreciable electrocardiographic change. The same was true of the glycoside of squill. Metrazol produced slight segment depression which continued for approximately sixty minutes, and, at the completion of our study, a noticeable increase in the positive polarity of the T wave was present. This change we are unable to explain. The effect of coramine was negligible.

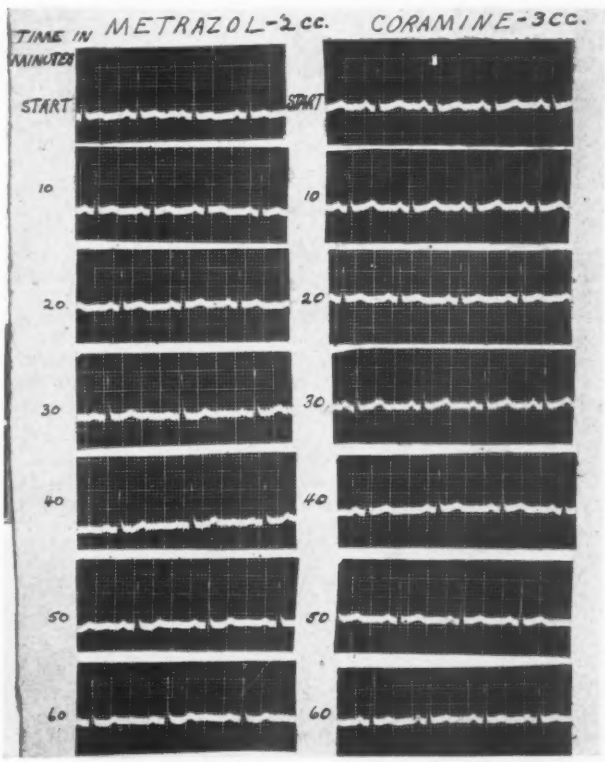

Fig. 15.—Serial electrocardiograms on cardiac glycosides, recorded in Lead II.

The foregoing observations suggest a selective electrocardiographic effect for at least some of the drugs used in this study. The actual significance of these observations is open to further investigation.

SUMMARY

1. Three cardiac glycosides, namely, cedilanid, digoxin and ouabain, produced appreciable and characteristic electrocardiographic changes within the two-hour period of observation.

2. The effects of cedilanid and digoxin were gradual, but the former produced a more significant change, quantitatively.

3. A fresh preparation of ouabain produced significant electrocardiographic change that can be considered maximum for this drug within ten minutes after administration.

4. This ouabain effect was two-thirds nullified at the end of two hours, whereas the effects of cedilanid and digoxin remained almost at their maximum until the study was completed.

5. The foregoing observations suggest that there is a selective action of these drugs on the electrocardiogram, and this selectivity warrants futher study.

6. Metrazol produced an electrocardiographic change which was unlike that produced by the glycosides.

REFERENCES

1. Pardee, H. E. B.: Clinical Observations on the Use of Intravenous Digitalis Preparations, J. A. M. A. **91**: 147, 1928.
2. Tandowsky, R. M.: An Electrocardiographic and Clinical Study of Lanatoside C, AM. HEART J. **24**: 472, 1942.
3. Cohn, A. E., Fraser, F. R., and Jamieson, R. A.: The Influence of Digitalis on the T Wave of the Human Electrocardiogram, J. Exper. Med. **21**: 593, 1915.
4. Larsen, K., Neukirch, F., and Nielsen, N. A.: Electrocardiographic Changes in Normal Adults Following Digitalis Administration, AM. HEART J. **13**: 163, 1937.
5. Geiger, A. J., Blaney, L. F., and Druckemiller, W. H.: A Quantitative Electrocardiographic Study of Digitalization, AM. HEART J. **21**: 230, 1941.
6. Stewart, H. J., and Watson, R. F.: The Effect of Digitalis on the Form of the Human Electrocardiogram With Special Reference to Changes Occurring in the Chest Lead, AM. HEART J. **15**: 604, 1938.
7. McMillan, T. M., and Bellet, S.: Diagnosis and Treatment of Cardiovascular Disease, Philadelphia, 1941, F. A. Davis Company, Chapt. 36.
8. Tandowsky, R. M.: Clarke, R. M.: Unpublished observations.
9. Rothschild, M. A., Mann, H., and Oppenheimer, B. S.: Successive Changes in the Electrocardiogram Following Acute Coronary Occlusion, Proc. Soc. Exper. Biol. & Med. **23**: 253, 1926.
10. Thompson, W. P.: The Electrocardiogram in the Hyperventilation Syndrome, AM. HEART J. **25**: 372, 1943.
11. Master, A. M., Friedman, R., and Dack, S.: The Electrocardiogram After Standard Exercise as a Functional Test of the Heart, AM. HEART J. **24**: 777, 1942.
12. Oettel, H.: Digitalis lanata. Klinisch gesehen: Tatsachen und Wertung, Med. Klin. **35**: 1628, 1939.
13. Gold, Harry, Cattell, McKeen, Kwit, Nathaniel, and Kramer, Milton: The Relative Activity of Digitalis Preparations in the Frog, the Cat, and Man, and Its Bearing on the Problem of Bio-Assay and So-Called Deterioration, J. Pharmacol. & Exper. Therap. **73**: 212, 1941.
14. Libow, I. M., and Feil, H.: Digitalis and the Normal Work Electrocardiogram, AM. HEART J. **22**: 683, 1941.
15. White, P. D., and Sattler, R. R.: The Effect of Digitalis on the Normal Human Electrocardiogram, With Especial Reference to A-V Conduction, J. Exper. Med. **23**: 613, 1916.
16. DeGraff, A. C., and Wible, C. L.: Production of Digitalis of T-Wave Changes Similar to Those of Coronary Occlusion, Proc. Soc. Exper. Biol. & Med. **24**: 1, 1926.
17. Stewart, H. J.: Effect of Giving Digitalis on the Volume Output of the Heart and Its Size in Normal Individuals, Proc. Soc. Exper. Biol. & Med. **29**: 207, 1931.
18. Strauss, Harry, and Katz, L. N.: Effect of Digitalis on the Appearance of Lead IV, AM. HEART J. **10**: 546, 1935.
19. Wegria, Rene, Geyer, J. H., and Brown, B. S.: The Fibrillation Threshold After the Administration of Digitalis and Ouabain, J. Pharmacol. & Exper. Therap. **71**: 336, 1941.

ON THE MECHANISM OF THE ELECTROCARDIOGRAPHIC SYNDROME OF SHORT P-R INTERVAL WITH PROLONGED QRS COMPLEX

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THE subject of this paper, namely, the electrocardiographic phenomenon of a short P-R interval followed by a prolonged QRS complex, has been heretofore judged to be of academic interest only. Actually, it is part of a syndrome manifested by heart consciousness which occurs in patients who have a tendency to paroxysmal arrhythmias. These ectopic rhythms may have their focal origins in either auricles or ventricles. Although they are often more annoying than dangerous, the fact that there is always a potential hazard was pointed out recently by Wood, Wolferth, and Geckeler,[1] who reported the sudden death of a boy of 13 years.

Knowledge of the mechanism of this peculiar syndrome is still in its hypothetic stage. The hypothesis advanced by Holzmann and Scherf[2] and Wolferth and Wood[3] is essentially as follows:

Some hearts possess, in addition to the normal conduction system, an aberrant pathway connecting one of the auricles with one of the ventricles. Through this aberrant pathway, early stimulation of one of the ventricles may occur. The relatively later spread of excitation to the other ventricle is the cause of the prolongation of the QRS complex.

This hypothesis was recently supported by the experimental evidence of Butterworth and Poindexter.[4] By short-circuiting the normal conduction system through an amplifier, they were able to reproduce the electrocardiographic picture in animals. In a recent communication,[5] clinicolaboratory evidence was presented in favor of this hypothesis. It was suggested that the QRS complex in the syndrome may, in some cases, be the result of simultaneous functional activity of the aberrant and normal pathways. Histologic proof of the existence of accessory conduction connections between the auricles and the ventricles of a patient with this type of electrocardiographic abnormality was recently furnished by Wood, Wolferth, and Geckeler.[1]

If the assumption of an aberrant conduction pathway is correct, it should be possible to modify conduction by means of drugs (or otherwise), either in it or the normal conduction tissue in such a manner as to obtain functional release of one or the other. Depression of the functional activity of the aberrant tissue should divert the electrical

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impulse exclusively through the A-V node, and, in so doing, rectify the conduction time relationships in the electrocardiogram. If, on the other hand, the A-V node could be depressed at a time when the electrocardiogram pattern is normal, the aberrant mechanism, being the sole pathway, should give rise to an electrocardiographic pattern consisting of abnormal complexes.

A case suitable for this sort of clinical investigation recently presented itself at Seaview Hospital.

H. W., a 31-year-old colored man, was admitted Feb. 12, 1942. His past history included pneumonia and influenza in childhood and gonorrhea in adolescence. For several years prior to admission, he had had occasional pains in various joints and had noted occasional palpitation on slight exertion. In November, 1941, he developed a cough with a small amount of yellowish sputum, asthenia, and loss of weight. In December, 1941, he was very ill, with elevation of his temperature to 103° F.

On physical examination, a dorsal scoliosis was noted. The lungs were normal clinically and roentgenographically. The heart sounds were of good quality and regular. The rate was 80 per minute. A soft systolic murmur was heard at the apex of the heart. Fluoroscopic examination revealed no abnormalities of the cardiovascular silhouette. The blood pressure was 140/80. There were no evidences of heart failure. The hands and feet were cool. The radial arteries were thickened. The blood cell counts were normal, the blood was normal from the chemical standpoint, and the blood Wassermann reaction was negative. Urinalysis showed a faint trace of albumin and an occasional erythrocyte and leucocyte. The electrocardiogram showed a short P-R interval with prolonged QRS complex (Fig. 1, *B*). The clinical course was uneventful. Many sputum and gastric examinations for acid-fast bacilli yielded negative results. The blood pressure was variable, and, at times, reached hypertensive levels (148, 164, systolic; and 118, 124, diastolic).

EXPERIMENTAL OBSERVATIONS

The following pertinent experimental observations were made over a period of three months:

1. On April 17, a control electrocardiogram showed a P-R interval of 0.08 second and a QRS time of 0.11 to 0.12 second. There was a notch on the upstroke of R_1, and also on the downstroke of R_3 at its summit. The heart rate was 68 to 75 per minute. Atropine sulfate (1.3 mg.) was given intravenously. Tracings were taken at short intervals for a period of fifteen minutes. The heart rate increased to 100 per minute. The voltage of the QRS complex increased in the standard leads. With the increase in voltage, the slur and notch on R_{1-3} were obliterated. The P-R interval and the duration of the QRS complex were not affected. Fifteen minutes after the administration of atropine, prostigmine methylsulfate (1 c.c. of 1:4,000 solution) was administered subcutaneously. Twenty minutes later the heart rate was 72. There was no other change in the electrocardiogram.

2. On April 17, 18, and 19, the patient was given a daily oral dose of 0.4 Gm. (4 cat units) of digitalis leaf. On April 20, the tracing showed his usual (abnormal) pattern in Leads I and II. In Lead III

there was an occasional altered (normal) beat, and, in Lead IV, regularly recurring complexes with a P-R interval of 0.16 second and a QRS time of 0.08 second were recorded. The RS-T_4 segment was elevated, and T_4 was diphasic. The record obtained April 21 is reproduced in Fig. 1, *A*, and that of April 22, in Fig. 1, *C*. This latter was the only record with reversed conduction relationships in all leads throughout the course of the observations except those obtained after the administration of quinidine.

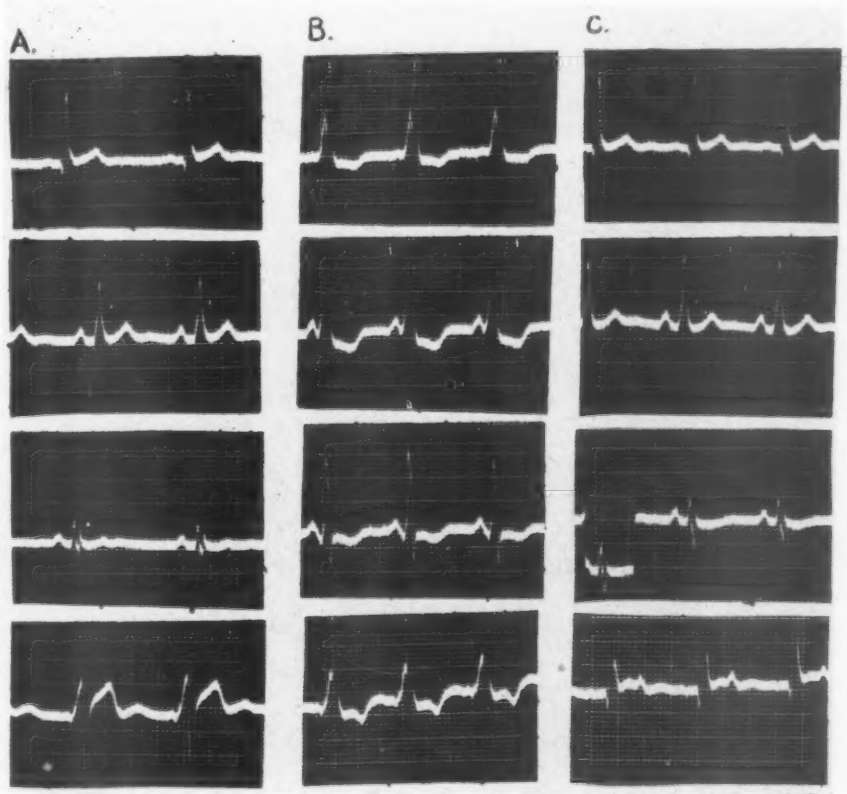

Fig. 1.—*A*, Leads I, II, and III show normal sinus rhythm. Lead IV shows a short P-R interval and a prolonged QRS complex. Lead IV differs, however, from the usual fourth lead in the abnormal tracings. *B*, The characteristic abnormal tracing. *C*, Normal sinus complexes in all four leads.

3. On April 24, 2 mg. of atropine sulfate were given intravenously. The heart rate increased from 75 per minute in the control record to 100 per minute. There was an increase in the voltage of the QRS complex in the standard leads, as observed previously after the administration of atropine. In a series of tracings taken over a period of twenty minutes, the rhythm remained the same. Twenty minutes after the administration of atropine, prostigmine methylsulfate (1 c.c. of 1:4,000 solution) was given intramuscularly. The heart rate decreased to 86 per minute with no other change.

4. On April 25, positional tracings were taken on deep inspiration and deep expiration. The electrocardiographic pattern remained abnormal in all tracings obtained. Structural changes occurred in the

R wave and in T_1. There were spontaneous variations in heart rate from 60 to 100 per minute. Some of the variations are recorded in Fig. 2.

5. Beginning April 30, the patient was given 0.4 Gm. (4 cat units) of digitalis leaf daily by mouth for four consecutive days. Daily electrocardiograms were secured. The only changes observed were exaggerated depression of the R-T segments in all leads and variations in rate (Fig. 3, *B* and *C*).

6. On May 8, the control tracing showed a heart rate of 75 per minute. $R\text{-}T_{1 \text{ and } 2}$ were still markedly depressed. Epinephrine (0.5 c.c. of a 1:1,000 aqueous solution) was administered intramuscularly. Tracings were obtained fifteen, twenty, and twenty-five minutes after the injection. Twenty minutes after the injection the heart rate was 50, which was the slowest rate ever observed in this case (Fig. 3, *A*).

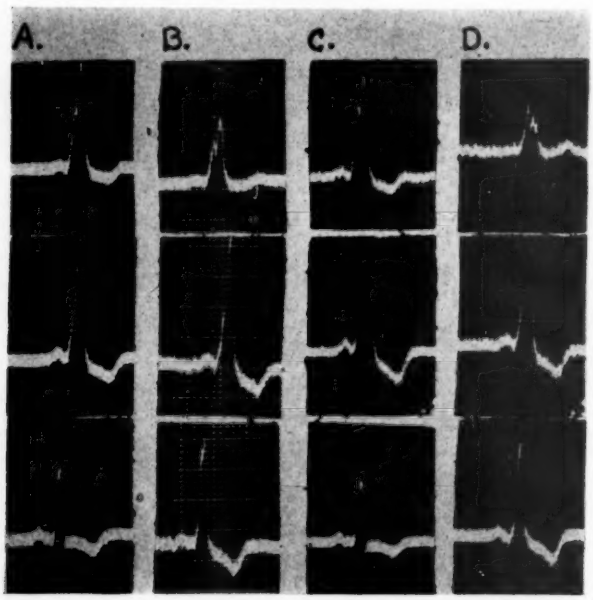

Fig. 2.—Positional tracings. *A*, Leads I, II, and III taken in the supine position. *B*, Leads I, II, and III taken in the supine position on deep inspiration. *C*, Leads I, II, and III taken in the right lateral position. *D*, Leads I, II, and III taken in the left lateral position.

7. On May 15, the control tracing showed a heart rate of 60 per minute. Mecholyl chloride (15 mg.) was given subcutaneously. A tracing obtained two minutes after the injection showed a rate of 100 and accentuation of the notch on the upstroke in Lead I, with concomitant lowering of the voltage of QRS_1, as if a change in the electrical axis had taken place. Seven minutes later, at the height of the systemic reactions due to mecholyl (sweating, lacrimation, and choking sensation), 2 mg. of atropine sulfate were given intravenously. The heart rate remained at 100 per minute, approximately the same as before the injection. The voltage of R_1 increased and the notch on the upstroke became less conspicuous. No other structural change in the electrocardiogram took place. An occasional premature ventricular contraction appeared.

8. On May 19, the patient was given an oral test dose of quinidine sulfate (0.2 Gm.), after which 0.4 Gm. was given orally every four hours. On May 20, he had 0.4 Gm. of quinidine at 8:00 A.M. and 0.8 Gm. at noon. In the two days he had received a total of 3.3 Gm. of the drug. An electrocardiogram taken at 3:00 P.M. showed a normal sinus pattern similar to the tracing reproduced in Fig. 1, *C*.

9. On May 22, the control tracing showed the usual (abnormal) characteristics. A single dose of 0.8 Gm. of quinidine sulfate was administered. A tracing obtained three and a half hours later again showed the normal sinus pattern.

10. On May 25, the control tracing showed the usual abnormality. Two and a half hours after a single dose of 0.8 Gm. of quinidine, a tracing revealed a normal pattern in all leads. At this time 4 c.c. of prostigmine methylsulfate (1:4,000) were given intramuscularly. A tracing taken fifteen minutes later was again abnormal. This took place approximately two hours and forty-five minutes after the administration of quinidine.

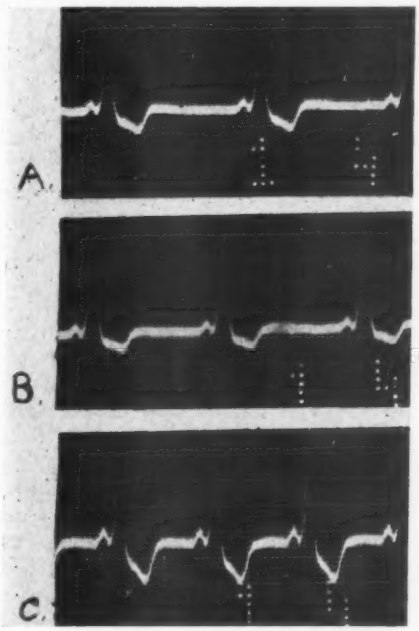

Fig. 3.—Lead II only. *A*, The effect of 0.5 c.c. of 1:1,000 epinephrine intramuscularly. *B*, Tracing taken after two daily doses of digitalis leaf, 0.4 Gm. each. *C*, Tracing taken after four daily doses of digitalis leaf, 0.4 Gm. each.

11. On May 27, control tracings were abnormal. A single dose of 0.8 Gm. of quinidine sulfate was given orally, and frequent tracings were taken in order to establish the time of onset and the duration of the expected change in conduction. It appeared two and a half hours after the administration of the drug and lasted two and a half hours thereafter.

12. On June 1, the control tracing was abnormal. A single dose of quinidine sulfate (0.8 Gm.) was given orally. Two hours later a tracing showed an alternating type of conduction (Fig. 4, *A* and *B*). The subsequent tracings were normal. Three hours and forty-five minutes

after the administration of quinidine (about one and a half hours after the onset of normal conduction), 4 c.c. of prostigmine methylsulfate (1:4,000) were given intramuscularly. The tracing taken fifteen minutes later was still normal. The next tracing, taken forty-five minutes after the injection of prostigmine, was abnormal.

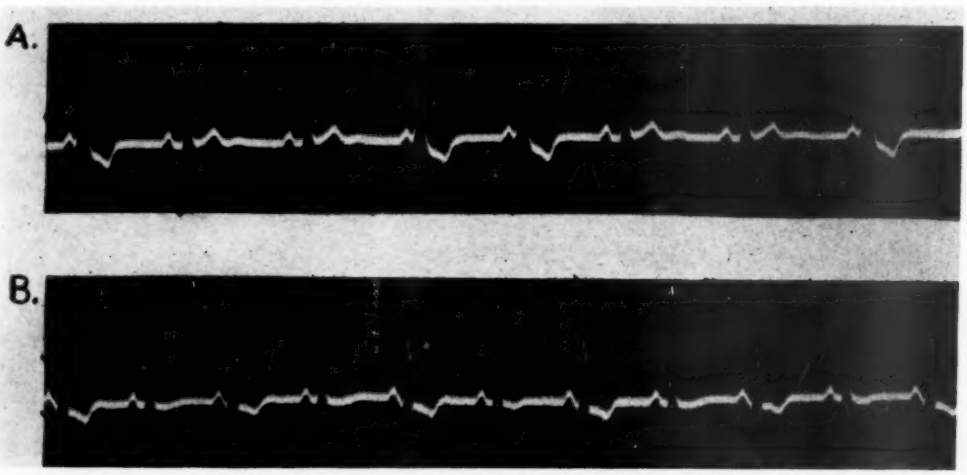

Fig. 4.—Alternating type of rhythm after quinidine. *A*, Lead II on one occasion. *B*, Lead III on another occasion.

13. On June 3, the control tracing was abnormal. Three hours after a single oral dose of quinidine sulfate (0.8 Gm.) the conduction was alternating. The three and one-half hour tracing was normal in all leads. Fifteen milligrams of mecholyl chloride were given subcutaneously about four hours after the administration of quinidine. Two minutes later the tracing still showed a normal conduction pattern, but the rate was faster. Ten minutes after the injection of mecholyl the conduction was alternating. At this point the systemic reactions due to mecholyl were so marked that atropine sulfate (1.2 mg.) was given intravenously. The tracing obtained immediately after the injection of atropine was again abnormal; the rate was slightly slower than in the control tracing. Fifteen minutes after the injection of atropine the rate was considerably slower than in the control (Fig. 5).

14. On June 4, the control tracing was abnormal. A single oral dose of 0.8 Gm. of quinidine sulfate was administered, and several tracings were taken at frequent intervals. The tracing was still abnormal three and a half hours after quinidine was given. It first became normal four hours after the administration of quinidine. Six cubic centimeters of digifolin (3 cat units) were then given intravenously. A tracing taken two minutes later was normal. Fifteen minutes after the injection of digifolin, the electrocardiogram was again abnormal. There was no other structural change in any of the segments of the QRS-T complex.

15. On June 5, quinidine (0.8 Gm.) again was given orally. A single tracing, obtained four hours later, showed normal conduction. The control had shown the usual abnormal characteristics.

16. On June 18, it seemed that the patient had become tolerant to quinidine. He was given 0.8 Gm. of the drug at 7:00 A.M. (before

breakfast). Frequent electrocardiograms were taken. Four hours and forty minutes after the administration of the drug, the tracing was still abnormal. He was given a second dose of 0.8 Gm. at 11:50 A.M. One hour later the electrocardiographic pattern was normal. At this time strophanthin K (0.25 mg. in 1 c.c.) was given intravenously. Serial tracings were taken immediately after the injection and for five hours subsequent to it. The conduction remained normal. No tracings were taken during the night. The following morning the conduction was again abnormal.

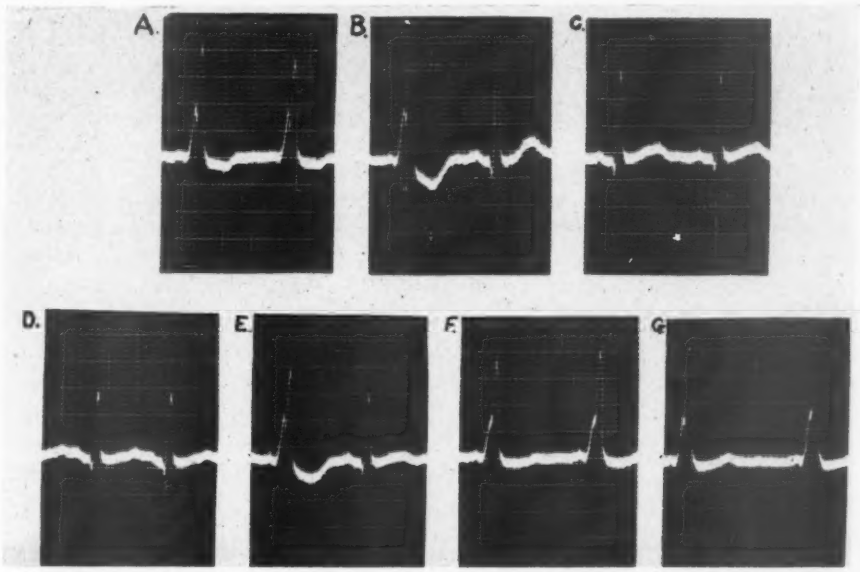

Fig. 5.—*A*, Control tracing. *B*, Alternating rhythm observed three hours after a single dose of quinidine (0.8 Gm.). *C*, Normal tracing three and one-half hours after administration of quinidine. *D*, Tracing obtained two minutes after 15 mg. of mecholyl subcutaneously. *E*, Alternating rhythm after injection of mecholyl. *F*, Abnormal tracing following injection of mecholyl. *G*, Tracing obtained fifteen minutes after injection of atropine. Note slow rate as compared with control tracing in *A*.

17. On June 22, four hours and fifteen minutes after a single dose of quinidine (0.8 Gm.), the electrocardiogram was still abnormal. A second dose of 0.4 Gm. was then administered. Forty-five minutes after the second dose the tracing was normal. Forty-five minutes later, strophanthin K (0.5 mg. in 10 c.c. of saline) was given intravenously. Tracings were taken at frequent intervals for one and one-half hours. The pattern remained normal. The next tracing, one hour later, was abnormal; it was taken two and one-half hours after the injection of strophanthin, or three hours and fifteen minutes after the conduction became normal.

18. Beginning June 25, the patient was given 0.4 Gm. of quinidine sulfate four times daily for a period of eight days. No medication was given during the night. Electrocardiograms were secured daily at about the same time (3:30 P.M.). A normal pattern was observed on one occasion only (June 30). The last two abnormal tracings showed an upright T_1.

19. On July 3, a single dose of quinidine sulfate (1.1 Gm.) was given at 7:00 A.M. A tracing secured at 10:30 A.M. was normal. Prostigmine

methyl sulfate (5 c.c. of 1:4,000 solution) was then administered intramuscularly. Tracings were taken at five-minute intervals. Fifteen minutes after the injection the patient appeared uncomfortable; his face was covered with beads of perspiration. The twenty-five-minute tracing was still normal, without even an appreciable change in the heart rate. Fifteen milligrams of mecholyl chloride were then administered subcutaneously. Two minutes later the heart rate increased from 70 to 120 per minute; the conduction, however, remained normal. Three minutes after the injection of mecholyl the patient's discomfort increased greatly. He perspired profusely, and developed a choking sensation and an intense desire to urinate. Two milligrams of atropine sulfate were immediately injected intravenously. Tracings were taken before, during, and after the injection. The conduction remained normal. The heart rate, however, decreased to 87 per minute within five minutes after the injection. Consecutive tracings at frequent intervals were normal until 2 P.M., when the first abnormal tracing was obtained (heart rate, 75 per minute). It differed from the control in that it showed extremely high voltage of the QRS complexes, apparently an effect of atropine, as observed previously.

COMMENT

During the three months the patient was under observation, 105 electrocardiograms were taken. On one occasion, a tracing showing normal sinus rhythm in all four leads was obtained three days after digitalis was discontinued. All other normal tracings apparently resulted from giving quinidine. Quinidine sulfate was given on twelve occasions; in doses of 0.8 Gm. or more it never failed to produce a normal sinus pattern. The effect of the drug was apparent as early as two hours after its administration. In the later observations (Experiments 16 and 17), a longer time was required for the effect to become manifest. It is quite possible that the element of time, rather than the second dose of the drug, was the determining factor in producing the normal electrocardiographic pattern in these experiments. The duration of the quinidine effect was at least two and one-half hours after a single dose of 0.8 Gm., and at least five hours when a second dose was given five hours after the unsuccessful, or insufficient, first dose. The effect of a single 1.1 Gm. dose was a normal conduction pattern which lasted at least three and one-half hours.

The effect of quinidine on this electrocardiographic phenomenon was previously reported by Roberts and Abramson.[6] Their observations were subsequently confirmed by Wolferth and Wood.[7] It is interesting that doses of 0.325 Gm. were ineffectual in the latter's case, whereas a double dose produced a normal pattern. It is evident that, in order to maintain the normal conduction pattern, large doses would have to be repeated at frequent intervals to balance the rate of absorption and the rate of excretion of the drug. The effect of quinidine is interesting from the physiologic point of view. It lends support to the hypothesis advanced by Holzmann and Scherf[2] and Wolferth and Wood[3] that the syndrome is due to the presence in some hearts of an aberrant conduction

mechanism which connects one of the auricles with one of the ventricles. Quinidine apparently has a pronounced affinity for the aberrant mechanism, and depresses it. Normal transmission of the sinus impulse then takes place through the A-V node, with the normal electrocardiographic pattern. On the other hand, any substance with a greater affinity for the A-V node will depress it and allow propagation of the sinus impulse through the aberrant mechanism, with the resulting abnormal electrocardiographic pattern.

The effect of digitalis on the syndrome was first noted by Scherf and Schönbrunner.[8] They observed an increase in the duration of the abnormal QRS complex after the administration of digitalis and ultimate disappearance of the abnormally conducted beats when the drug was continued. They concluded that the abnormal conduction mechanism is more susceptible to the effects of digitalis than the specific conduction tissue.

In a recent communication,[5] a more detailed study of the effect of digitalis on the syndrome was reported. An increase in the duration of the abnormal QRS complex was produced by the drug, and evidence was presented to indicate that the phenomenon is vagal in character. The effect of digitalis on the abnormal complex was interpreted as indicating increased asynchronism of ventricular stimulation due to the cholinergic properties of the drug, particularly to its depressing effect on the A-V node. The usual abnormal complex was thought to be a compromise effect of the simultaneous functional activity of the A-V node and the aberrant tissue.

In the case herewith presented, no such effect of digitalis on the abnormal complex was observed. When administered (intravenously), however, at a time when the aberrant conduction tissue was depressed and the conduction pattern was normal, it caused reappearance of the abnormal complex. Other cholinergic drugs, namely, prostigmine and mecholyl, had a similar action. Since the transformation of the normal conduction pattern to the abnormal one was accomplished soon after a normal pattern was established, it is hardly possible that this could have been spontaneous. The failure of the combined action of mecholyl and prostigmine to reproduce the abnormal pattern in Experiment 19 may be explained by the marked depression of the aberrant tissue caused by a large dose of quinidine (1.1 Gm.). The double dose of quinidine in Experiments 16 and 17 was probably the cause of the failure of strophanthin to produce the abnormal conduction pattern. The struggle between the A-V node and the aberrant tissue in this case did not result in a compromise modification of the QRS complex, but rather in a surrender of the functional activity of one or the other mechanisms.

The presence of exaggerated vagal tone in cases of this syndrome is supported by the following additional evidence: sinus arrhythmia of greater or lesser extent was almost universally present in all the abnormal tracings. The heart rate was subject to spontaneous fluctuations

from 60 to 100 per minute (Fig. 3, *B* and *C*). Even when the vagus was not in full control (Fig. 4), an arrhythmia manifested itself in the relation of the abnormal groups to the normal ones and also in their relationship to each other. After an injection of epinephrine, the patient behaved like an animal with its vagi intact; his heart slowed—a phenomenon supposed to be reflexly mediated through the carotid sinus and aortic nerves and caused by elevation of the blood pressure. The slowing of the heart rate produced by atropine after mecholyl is probably of the same nature, and is caused by the rise in blood pressure.

SUMMARY

A case of short P-R interval and prolonged QRS complex is presented.

On repeated occasions the abnormal electrocardiogram was transformed into a normal one by the oral administration of quinidine.

Cholinergic drugs, including digitalis, when administered soon after the appearance of the normal electrocardiographic pattern, reproduced the abnormal pattern.

These observations are in harmony with the hypothesis that the abnormal electrocardiographic pattern is due to an accessory auriculoventricular conduction mechanism. Quinidine sulfate apparently has a greater affinity for the accessory tissue, and depresses it, thus allowing transmission of the sinus impulse through the normal pathway, whereas the cholinergic drugs (including digitalis), by depressing the A-V node, divert the impulse through the aberrant conduction tissue.

We wish to acknowledge the help of Lieutenant Colonel Irving S. Wright and Major Delavan V. Holman in the preparation of this paper.

REFERENCES

1. Wood, F. C., Wolferth, C. C., and Geckeler, G. D.: Histologic Demonstration of Accessory Muscular Connections Between Auricle and Ventricle in a Case of Short P-R Interval and Prolonged QRS Complex, AM. HEART J. **25**: 454, 1943.
2. Holzmann, M., and Scherf, D.: Ueber Elektrokardiogramme mit verkürzter Vorhof-Kammer-Distanz und positiven P-Zacken, Ztschr. f. klin. Med. **121**: 404, 1932.
3. Wolferth, C. C., and Wood, F. C.: The Mechanism of Production of Short P-R Intervals and Prolonged QRS Complexes in Patients With Presumably Undamaged Hearts: Hypothesis of an Accessory Pathway of Auriculo-Ventricular Conduction (Bundle of Kent), AM. HEART J. **8**: 297, 1933.
4. Butterworth, J. S., and Poindexter, C. A.: Short P-R Interval Associated With a Prolonged QRS Complex: A Clinical and Experimental Study, Arch. Int. Med. **69**: 437, 1942.
5. Fox, T. T., Travell, J., and Molofsky, L.: Action of Digitalis on Conduction in the Syndrome of Short P-R Interval and Prolonged QRS Complex, Arch. Int. Med. **71**: 206, 1943.
6. Roberts, G. H., and Abramson, D. I.: Ventricular Complexes of the Bundle-Branch-Block Type Associated With Short P-R Intervals, Ann. Int. Med. **9**: 983, 1936.
7. Wolferth, C. C., and Wood, F. C.: Further Observations on the Mechanism of the Production of a Short P-R Interval in Association With Prolongation of the QRS Complex, AM. HEART J. **22**: 450, 1941.
8. Scherf, D., and Schönbrunner, E.: Beiträge zum Problem der verkürzten Vorhof-Kammer-Leitung, Ztschr. f. klin. Med. **128**: 750, 1935.

CLINICAL EXPERIENCE WITH DICUMAROL

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THE prothrombin-lowering principle of spoiled sweet clover, 3,3′-methylene-*bis*-(4-hydroxycoumarin), was isolated, identified, and synthesized by Link and his co-workers.[1-4] The synthetic preparation, dicumarol, was first used in man by Butt, Allen, and Bollman,[5] and by Bingham, Meyer, and Pohle.[6] Both groups of investigators suggested that giving small doses of the drug daily was more effective than a single large dose, and that dicumarol might be used as a substitute for heparin in the prevention of thrombosis. Meyer, Bingham, and Pohle[7] recommended an initial oral dose of 5 mg. per kg. of body weight, followed by 1 to ⅕ mg. per kg. daily.

This report is based on the study of thirty patients with thromboembolic diseases (Table I). There were fourteen cases of peripheral arterial occlusion (six femoral, two popliteal, two axillary, one brachial, two thromboangiitis obliterans, one arteriosclerosis obliterans); one case of coronary artery occlusion; four cases of cerebral artery occlusion (two embolic, associated with rheumatic heart disease, and two thrombotic); two cases of subacute bacterial endocarditis; four cases of pulmonary artery occlusion; one case of retinal vein thrombosis; three cases of thrombophlebitis; and one case of what was probably hepatic vein thrombosis.

METHOD OF STUDY

Twenty-five patients received 300 mg. of dicumarol orally on each of the first two days, and 50 mg. daily thereafter. The drug was discontinued when the first indication of hemorrhage appeared. Five patients received 200 mg. every other day; the intervals were prolonged when the prothrombin was considered to be dangerously low. The average predosage levels were: plasma prothrombin, 80 per cent; clotting time, four minutes; bleeding time, two minutes. In all cases a control determination of plasma prothrombin, venous clotting time, and bleeding time were made just prior to the administration of dicumarol and at frequent intervals throughout the therapeutic period. In many cases, similar observations were made with respect to the leucocyte count, hemoglobin, blood sugar, blood urea nitrogen, van den Bergh, icterus index, bromsulfalein retention, and urine specific gravity, albumin, sugar, and formed elements.

Plasma Prothrombin.—Quick's[8] method was used for determining the plasma prothrombin, and the results were expressed in percentage of

From the Philadelphia General Hospital.

From the Committee for the Study of Dicumarol, which includes G. Mason Astley, M.D., Col. Thomas Fitz-Hugh, Jr., M.C., U. S. A., Thomas M. McMillan, M.D., and the authors. The authors acknowledge the cooperation of the visiting physicians on whose services the patients were treated.

The dicumarol was supplied by Eli Lilly and Co., Indianapolis, Ind.

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TABLE I

SUMMARY OF PATIENTS TREATED WITH DICUMAROL

DIAGNOSIS	NUMBER OF CASES	RECOVERED	DIED	CASE NUMBER	REMARKS
1. Peripheral arterial occlusion a. Femoral	6	*		1	Arteriosclerotic heart disease; auricular fibrillation; embolectomy; slight wound, bleeding on the third day; prothrombin, 20 per cent
		*		2	Gunshot perforation of femoral artery; massive hematoma; surgical repair; no toxicity
			*	3	Arteriosclerotic heart disease; died within twenty-four hours
			*	4	Arteriosclerotic heart disease; diabetes mellitus; no toxicity
		*		5	Gangrene of toes (body cast for fractured femur); 200 mg. every other day for 34 doses; improved circulation; no toxicity
		*		6	Gangrene of toe; 200 mg. every other day; no toxicity
b. Popliteal	2	*		7	Gangrene of toes; amputation; no toxicity
		*		8	Slight circulation improvement; no toxicity
c. Brachial	1	*		9	Arteriosclerotic heart disease; gangrene on tips of two fingers; slow improvement; rectal bleeding on twelfth day; prothrombin, 11 per cent; clotting time, five minutes
d. Axillary	2	*		10	Rheumatic heart disease; auricular fibrillation; 200 mg. every other day; no toxicity
			*	11	Arteriosclerotic heart disease; heart block; diabetes mellitus; died within twenty-four hours; no toxicity
e. Thromboangiitis obliterans	2	*		12	Slight temporary improvement; leg amputation later; no toxicity
		*		13	Slight improvement in one leg; 200 mg. every other day for three weeks; no toxicity
f. Arteriosclerosis obliterans	1	*		14	No improvement, leg amputation later; no toxicity
2. Coronary artery occlusion	1		*	15	Died on nineteenth day; prothrombin, 100 per cent at death; no toxicity
3. Cerebral artery occlusion a. Embolic	2	*		16	Rheumatic heart disease; congestive failure, no toxicity
		*		17	Rheumatic heart disease; auricular fibrillation; slow improvement; small episcleral hemorrhage on sixth day; bleeding time six minutes; clotting time, six minutes; prothrombin 8 per cent

TABLE I—CONT'D

DIAGNOSIS	NUMBER OF CASES	RECOVERED	DIED	CASE NUMBER	REMARKS
b. Thrombotic	2	*		18	Hypertensive heart disease; diabetes mellitus; slow improvement; no toxicity
			*	19	Died in four days; blood not clotted at autopsy table, twelve hours after death
4. Subacute bacterial endocarditis	2		*	20	Died after two months' treatment; no toxicity
			*	21	Died in three days; no toxicity
5. Pulmonary artery occlusion	4	*		22	Auricular fibrillation; no toxicity
		*		23	Secondary to phlebitis; no toxicity
		*		24	Following cesarean section; hematuria and vaginal bleeding on eighth day; prothrombin, 8 per cent; clotting time, ten minutes; one blood transfusion
		*		25	Small hemorrhages of feet two weeks after treatment begun; prothrombin 47 per cent; 200 mg. every other day for thirty-five days
6. Retinal vein thrombosis	1	*		26	Progressive improvement; no toxicity
7. Thrombophlebitis	3	*		27	Pelvic inflammatory disease, phlebitis of leg; improved rapidly; no toxicity
		*		28	Prompt improvement; no toxicity
		*		29	Good results; no toxicity
8. Hepatic vein thrombosis	1	*		30	Acute phlebitis of leg twelve days post partum; enlarged liver; abdominal distention; prominent superficial abdominal veins; 200 mg. every other day; no toxicity
Totals	30	23	7		

the average normal. Acetone-treated rabbit brain served as thromboplastin, and, with normal plasma, gave prothrombin times of eleven to thirteen seconds.

Venous Clotting Time.—Five cubic centimeters of venous blood were withdrawn into a sterile, dry syringe and quickly transferred to a chemically clean, dry test tube which was gently tilted every thirty seconds until the entire sample no longer flowed. The venous clotting time was recorded as the time which elapsed from the moment the blood was shed to when it congealed.

Bleeding Time.—The finger tip was pricked, and the time the drop of blood took to clot sufficiently to close the puncture in the skin and stop the bleeding was noted. The moment when bleeding ceased was taken as the end point.

RESULTS

Of the thirty patients treated, twenty-three recovered and seven died (Table I). Analysis of the deaths reveals that no toxic manifestations due to the drug were observed in any. Two were treated for femoral artery occlusion, one for axillary artery occlusion, one for coronary

artery occlusion, one for cerebral thrombosis, and two for subacute bacterial endocarditis. It is difficult to say whether or not the dicumarol contributed to the fatal outcome in any of these. It is our impression, however, that the disease pursued its natural course. It is equally difficult to credit the drug with contributing to recovery in our cases with a favorable outcome, although evidence is extant in this direction. Observations on the peripheral circulation were made by one of us (D. W. K.[9]). Oscillometric readings were made in eight cases; in five there was slight improvement, and in three, no appreciable effect on the larger arteries. In one case, there was definite improvement on the uninvolved side. With the histamine test, six of the eight patients showed improvement, two of whom showed definite improvement in the peripheral circulation by capillary response. When the larger arterial trunks are involved with thrombotic formation, the oscillometer will usually not demonstrate much improvement unless an appreciable amount of arteriospasm is present. The histamine test, however, is more likely to detect improvement in the distal capillary circulation.

Prothrombin.—Fig. 1 represents the results of determinations of plasma prothrombin in terms of percentage of normal in the patients who received 300 mg. daily for two days and 50 mg. daily thereafter. Three patients received dicumarol for as long as forty-four, fifty, and fifty-three days, respectively, with no evidence of cumulative or toxic effect. The curve which rises rapidly to a sustained prothrombin level of 100 per cent (Case 15) is difficult to interpret. Considering expected effect, the probable explanation for this is failure of absorption of the drug.

The broken line shows prompt restoration of the prothrombin eight days after withdrawal of the drug, which began when the prothrombin was 8 per cent (Case 24). One blood transfusion was given. In four cases, the prothrombin dropped to less than 10 per cent of normal, and transient hemorrhage occurred in two of these (Cases 17 and 24).

Fig. 2 (curve *A*) is a composite derived from a spot graph of Fig. 1. Although it fails to indicate the indubitably present latent period (because of insufficient determinations of prothrombin after twenty-four hours of treatment), it shows a rapid reduction of the prothrombin to a level of 25 to 30 per cent in two to three days, a maximum reduction in four to seven days, and then a slow, progressive rise to a level of about 50 per cent in four weeks, where it was subsequently maintained. The prothrombin was 20 per cent or less from the fourth to the ninth days.

Clotting Time.—Fig. 3 shows the results of the various clotting time determinations. These vary less markedly than do the prothrombin changes. The single clotting time of twelve minutes is associated with a prothrombin of 18 per cent, and the one of ten minutes with a prothrombin of 8 per cent. The broken line represents the return to a normal clotting time level of four minutes, eight days after cessation of the drug (Case 24). This is in general agreement with the observations of Quick,[10] who found the coagulation time relatively little delayed until

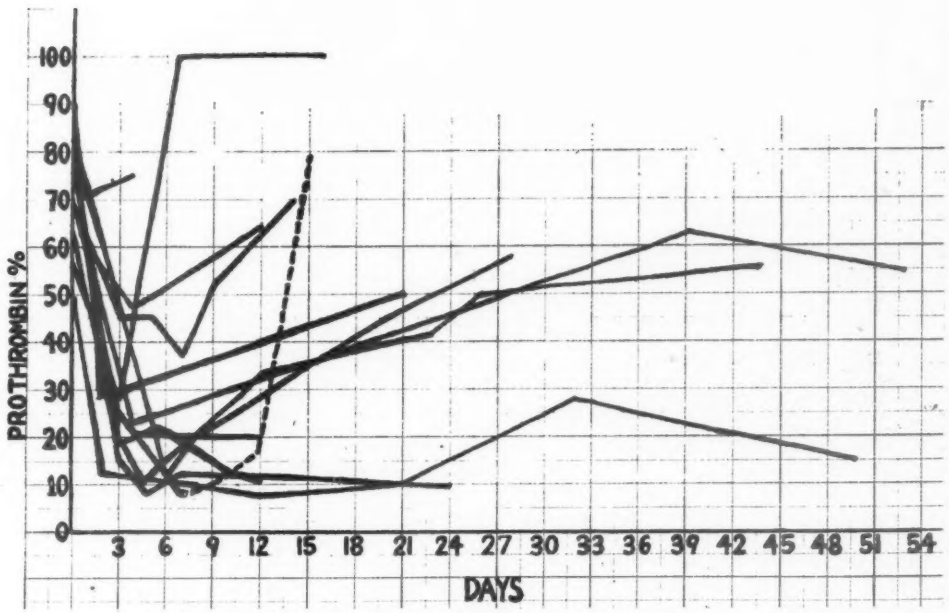

Fig. 1.—Prothrombin determinations during oral dicumarol dosage of 300 mg. daily for two days, followed by 50 mg. daily. The broken line (Case 24) represents prothrombin percentage after cessation of dicumarol therapy and one blood transfusion.

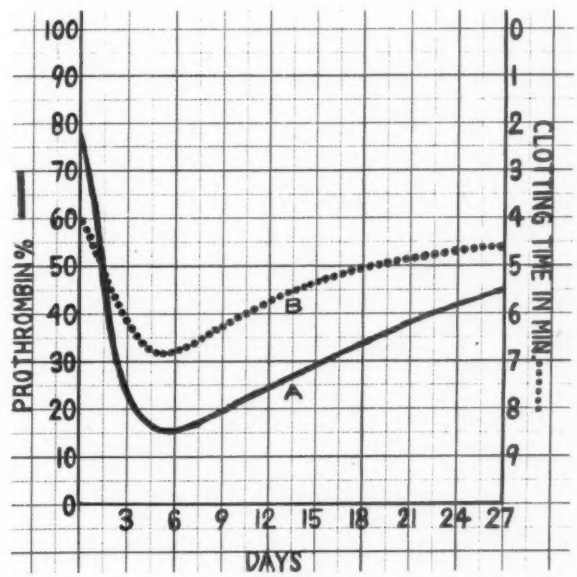

Fig. 2.—Comparison of composite curves of prothrombin percentage and clotting time (obtained from spot graphs of Figs. 1 and 3 respectively), showing quantitative difference and close parallel.

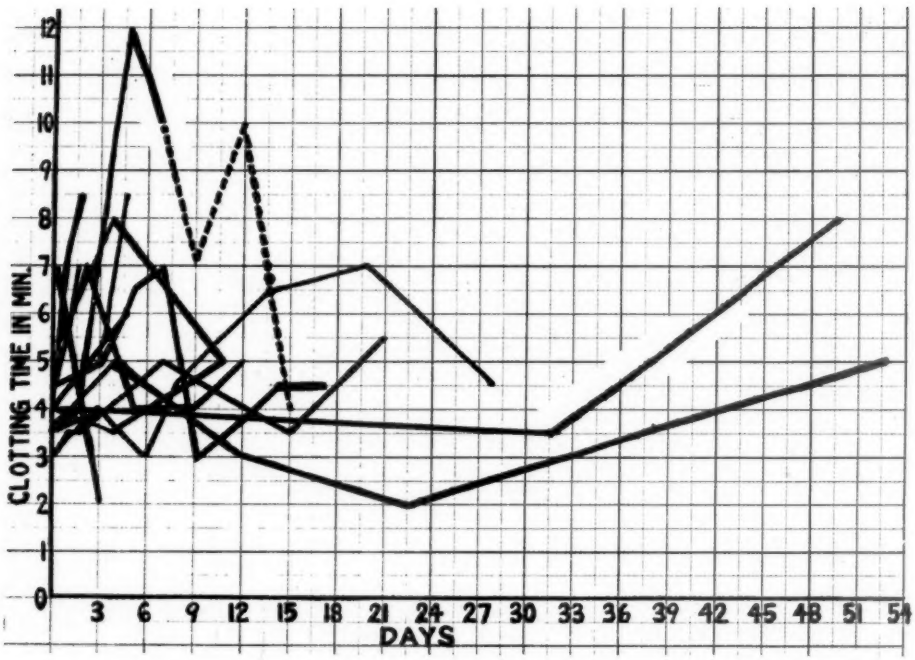

Fig. 3.—Clotting time determinations during the study. The broken line (Case 24) represents determinations after cessation of dicumarol therapy and one blood transfusion.

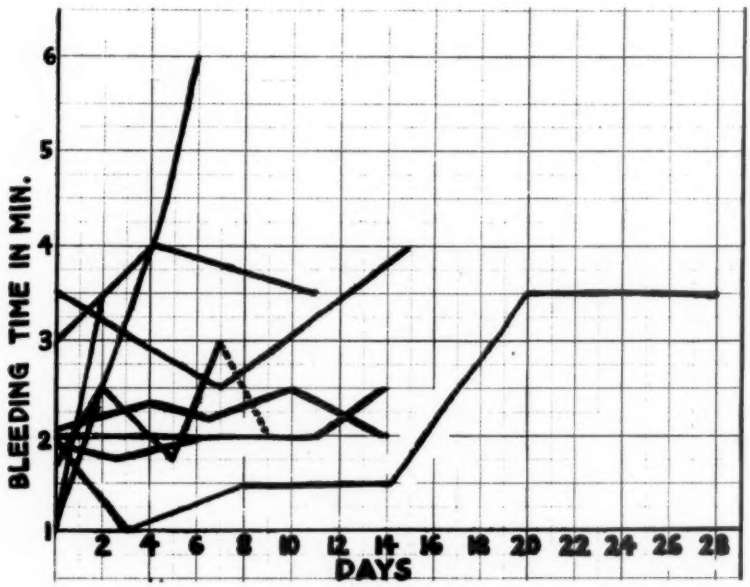

Fig. 4.—Bleeding time determinations, showing, by inspection, lack of significant alterations.

the prothrombin content dropped below 20 per cent of normal. Barker, Butt, Allen, and Bollman[11] reported that an increase in coagulation time usually occurred, but was considerably less constant than the effect on the prothrombin time.

Fig. 2 (curve *B*) is a composite of Fig. 3, and shows a rapid increase in clotting time to a level of six minutes in two to three days, a maximum increase from four to seven days, and then a gradual return to a level slightly greater than normal in about four weeks. The clotting time is six minutes or more from the third to the tenth days. This curve parallels the prothrombin curve rather closely (Fig. 2).

Bleeding Time.—The results of the bleeding time determinations (Fig. 4) are very variable. No pathologic level was observed, except the one of six minutes, at which time the prothrombin was 8 per cent (Case 17). This conforms with the observations of Allen, Barker, and Waugh[12] that the bleeding time is not influenced by dicumarol, and with those of Wright and Prandoni[13] that there is considerable variation in the bleeding time.

TOXICITY

No changes attributable to the dicumarol were observed in the leucocyte count, hemoglobin, blood sugar, blood urea nitrogen, van den Bergh, icterus index, bromsulfalein retention, and urine specific gravity, albumin, sugar, and formed elements. The effect on plasma prothrombin, venous clotting time, and bleeding time have been discussed. Schofield[14] found that spoiled sweet clover produced no abnormality of calcium or fibrinogen. No increase in antithrombin or decrease in platelets was noted by Roderick.[15] Quick[10] observed no alteration in any coagulation factor except prothrombin. Allen, Barker, and Waugh[12] reported an increased sedimentation rate and retarded clot retraction as a result of dicumarol. The latter observation was confirmed by Wright and Prandoni,[13] who, however, found no sedimentation rate changes, no increase in capillary fragility, and no hepatic or renal damage. Butt, Allen, and Bollman[5] reported no change in hemoglobin, erythrocyte count, leucocyte count, erythrocyte fragility, blood typing, serum bilirubin, or urine. Davidson and MacDonald[16] noted no alteration in plasma proteins.

The only toxic manifestations in our series were hemorrhagic phenomena (Table II) in five cases. On the third day after leg amputation, slight wound bleeding occurred (Case 1). Although the prothrombin was 20 per cent at this time, the complication may have been coincidental. Rectal bleeding occurred on the twelfth day of treatment for brachial artery occlusion (Case 9). The prothrombin was 11 per cent, and the clotting time, five minutes. A small episcleral hemorrhage developed (Case 17) on the sixth day of treatment, at which time the prothrombin was 8 per cent, the clotting time, six minutes, and the bleeding time, six minutes. On the eighth day after cesarean section (Case 24), hematuria

TABLE II

TOXICITY OF DICUMAROL

CASE NUMBER	HEMORRHAGIC MANIFESTATION	DAY OF APPEARANCE	PROTHROMBIN (%)	CLOTTING TIME (MIN.)	BLEEDING TIME (MIN.)
1	Postamputation wound bleeding	3	20	--	--
9	Rectal bleeding	12	11	5	--
17	Small episcleral hemorrhage	6	8	6	6
24	Postcesarean section hematuria and vaginal bleeding	8	8	10	3
25	Small hemorrhagic extravasations of feet	14	47	--	--

and vaginal bleeding occurred. The prothrombin was 8 per cent, the clotting time, ten minutes, and the bleeding time, three minutes. Small hemorrhagic extravasations on both feet developed on the fourteenth day, when the prothrombin was 47 per cent (Case 25). All five patients recovered promptly; dicumarol was discontinued immediately after evidence of toxicity was discovered. The patient with the hematuria and vaginal bleeding improved more slowly than the others, and required a whole blood transfusion.

Although the basic causative factor in the bleeding is defective coagulation due to prothrombin reduction, a possible added factor may be the extensive dilatation of small vessels noted by Bingham, Meyer, and Pohle[6] in animals which were receiving fatal doses of dicumarol. Duration of treatment is not a factor in toxicity, as indicated by the absence of ill effect in the three patients of our series who received the drug continuously for six to seven weeks. As much as 10 Gm. of dicumarol have been given over a ninety-two-day period without detectable changes in liver function.[17]

COMMENT

Since the risk of hemorrhage becomes distinct when the prothrombin is 20 per cent or less, it seems desirable to avoid the danger zone, from the third to ninth days (Fig. 2), by employing less drug during the first two days. The rising portion of the prothrombin curve might be explained by an increased tolerance to the drug, but it seems more reasonable to attribute it to the fact that the maintenance dose was approximately 1 mg. per kg., rather than the recommended 1.5 mg. per kg. The progressive increase in prothrombin to a level of 50 per cent seems undesirable because of the associated reduction in clotting time to an almost normal level.

A better dosage regime, therefore, might be 300 mg. of dicumarol on the first day, and 100 mg. thereafter. Although this schedule might produce a prothrombin curve more closely approximating the desired

one than does the authors' curve, it must be realized that, at best, it is only a rough guide toward dosage, and that the only reliable method of adjusting the daily dicumarol dose is by the results of frequent plasma prothrombin determinations.

There are a few large series reported on the use of dicumarol in normal persons to prevent thrombosis and embolism postoperatively,[11, 12, 18, 19] and several small series on the use of dicumarol in thrombo-embolic diseases.[11, 13, 20, 21] As with our results, the majority of reports are encouraging. Most investigators are agreed upon the absence of effect of dicumarol on the liver, kidney, or blood, except for the significant effect on prothrombin and clotting time. Hemorrhagic phenomena have been the only form of toxicity reported in man.

An obvious question which arises is, can the reduction of plasma prothrombin, particularly with the less marked alteration of venous clotting time, actually prevent intravascular clotting? There is experimental evidence for an affirmative answer. Allen, Barker, and Waugh[12] and Wright and Prandoni[13] observed retardation of clot retraction after dicumarol therapy. Bollman and Preston[22] noted a definite reduction in the tendency to thrombosis in glass cannulae inserted into carotid and femoral arteries of dicumarolized dogs. Dale and Jaques[23] made similar observations in veins crushed on a linen thread and in glass cells inserted between carotid artery and jugular vein. Richards and Cortell[24] found marked inhibition of thrombus formation in veins into which a selerosing solution had been injected.

Contraindications to the use of dicumarol:

1. Subacute bacterial endocarditis, when there is already a natural tendency toward hematuria and central nervous system bleeding.[12]

2. Renal insufficiency, especially with urinary suppression. In this situation there is an exaggerated response to dicumarol.[12]

3. Blood dyscrasia in which the hemorrhagic diathesis is already present.

4. Liver damage with vitamin K deficiency, when the prothrombin concentration is already reduced and difficult to restore,[12, 19] and the effect on the prothrombin is more marked than in a patient without liver disease.[25]

5. Ulcerating or granulating lesions, because of the tendency to bleeding in such cases.[11, 18]

Indications for dicumarol:

1. To prevent postoperative thrombosis and embolism.

2. To prevent extention of a thrombus already formed, and, secondarily, improve blood circulation.

Disadvantages of dicumarol:

1. Start of the action is delayed twenty-four hours or more. This may be overcome by using heparin for the first thirty-six hours, until the full effect of dicumarol has developed.[17, 26, 27]

2. Increased clotting time persists several days after cessation of dicumarol therapy, and can be corrected only temporarily by blood transfusion.

3. Factor of capillary dilatation. This is probably not of practical importance because it was demonstrated only in animals which received a massive, fatal dose of the drug.

4. Prothrombin must be dangerously low before the clotting time is sufficiently altered. Therefore, facilities must be available for carrying out the frequent prothrombin determinations that are essential for safe regulation of the dicumarol dosage.

Advantages of dicumarol over heparin:

1. Effective when given by mouth.
2. Prolonged action.
3. Low cost.

SUMMARY

1. Thirty patients with thrombo-embolic diseases were treated with dicumarol.

2. No changes were observed in the leucocyte count, hemoglobin, blood sugar, blood urea nitrogen, van den Bergh, icterus index, bromsulfalein retention, and urine specific gravity, albumin, sugar, and formed elements.

3. On the dosage schedule of 300 mg. orally for two days and 50 mg. daily thereafter, the plasma prothrombin fell rapidly from 80 per cent to 25 per cent of normal in three days, was 20 per cent or less from the fourth to ninth days, and then rose slowly to a level of 50 per cent in four weeks, where it was subsequently maintained. Coincidentally, the clotting time rose from four minutes to a level of six minutes in three days, was six minutes or more from three to ten days, and then fell slowly to a level slightly greater than normal in four weeks. The bleeding time was uninfluenced.

4. Of the thirty patients, seven died and twenty-three recovered. Improvement in the peripheral vascular circulation was demonstrated in six of eight cases studied.

5. Hemorrhage, the sole manifestation of toxicity, was observed in five cases, in all of which the patient recovered.

6. The only reliable method of ascertaining the proper dose of dicumarol is by frequent plasma prothrombin determinations.

REFERENCES

1. Campbell, H. A., Roberts, W. L., Smith, W. K., and Link, K. P.: Studies of the Hemorrhagic Sweet Clover Disease: I. The Preparation of Hemorrhagic Concentrates, J. Biol. Chem. **136**: 47, 1940.
2. Campbell, H. A., Smith, W. K., Roberts, W. L., and Link, K. P.: Studies on the Hemorrhagic Sweet Clover Disease: II. The Bioassay of Hemorrhagic Concentrates by Following the Prothrombin Level in the Plasma of Rabbit Food, J. Biol. Chem. **138**: 1, 1941.

3. Campbell, H. A., and Link, K. P.: Studies on the Hemorrhagic Sweet Clover Disease: IV. The Isolation and Crystallization of the Hemorrhagic Agent, J. Biol. Chem. **138**: 21, 1941.
4. Stahmann, M. A., Huebner, C. F., and Link, K. P.: Studies of the Hemorrhagic Sweet Clover Disease: V. Identification and Synthesis of the Hemorrhagic Agent, J. Biol. Chem. **138**: 513, 1941.
5. Butt, H. R., Allen, E. V., and Bollman, J. L.: A Preparation From Spoiled Sweet Clover [3,3′-Methylene-Bis-(4-Hydroxycoumarin)] Which Prolongs Coagulation and Prothrombin Time of the Blood: Preliminary Reports of Experimental and Clinical Studies, Proc. Staff Meet., Mayo Clin. **16**: 388, 1941.
6. Bingham, J. B., Meyer, O. O., and Pohle, F. J.: Studies on the Hemorrhagic Agent 3,3′-Methylene-Bis-(4-Hydroxycoumarin): I. Its Effect on the Prothrombin and Coagulation Time of the Blood of Dogs and Humans, Am. J. M. Sc. **202**: 563, 1941.
7. Meyer, O. O., Bingham, J. B., and Pohle, F. J.: The Effect of the Synthetic Dicoumarin, 3,3′-Methylene-Bis-(4-Hydroxycoumarin) on the Prothrombin Time and Coagulation Time, J. A. M. A. **118**: 1003, 1942.
8. Quick, A. J.: Nature of Bleeding in Jaundice, J. A. M. A. **110**: 1658, 1938.
9. Kramer, D. W.: Unpublished data.
10. Quick, A. J.: The Coagulation Defect in Sweet Clover Disease and in the Hemorrhagic Chick Disease of Dietary Origin, Am. J. Physiol. **118**: 260, 1937.
11. Barker, N. W., Butt, H. R., Allen, E. V., and Bollman, J. L.: The Effect of 3,3′-Methylene-Bis-(4-Hydroxycoumarin) on Blood Coagulation Factors, J. A. M. A. **118**: 1003, 1942.
12. Allen, E. V., Barker, N. W., and Waugh, J. M.: A Preparation From Spoiled Sweet Clover, J. A. M. A. **120**: 1009, 1942.
13. Wright, I. S., and Prandoni, A.: The Dicoumarin 3,3′-Methylene-Bis-(4-Hydroxycoumarin), J. A. M. A. **120**: 1015, 1942.
14. Schofield, F. W.: Damaged Sweet Clover; The Cause of a New Disease in Cattle Simulating Hemorrhagic Septicemia and Blackleg, J. Am. Vet. M. A. **64**: 553, 1924.
15. Roderick, L. M.: A Problem in the Coagulation in the Blood; ''Sweet Clover Disease of Cattle,'' Am. J. Physiol. **96**: 413, 1931.
16. Davidson, C. S., and MacDonald, H.: A Critical Study of the Action of 3-3′-Methylenebis (4-Hydroxycoumarin) (Dicoumarin), Am. J. M. Sc. **205**: 24, 1943.
17. Bingham, J. B., Meyer, O. O., and Howard, B.: Studies on the Hemorrhagic Agent 3,3′-Methylenebis (4-Hydroxycoumarin) III. A Report on Further Clinical Observations, Am. J. M. Sc. **205**: 587, 1943.
18. Butsch, W. L., and Stewart, J. D.: Clinical Experiences With Dicoumarin, J. A. M. A. **120**: 1025, 1942.
19. Meyer, O. O., Bingham, J. B., and Axelrod, V. H.: Studies on the Hemorrhagic Agent 3,3′-Methylene-Bis-(4-Hydroxycoumarin): II. The Method of Administration and Dosage, Am. J. M. Sc. **204**: 11, 1942.
20. LeFevre, F. A.: Effect of 3,3′-Methylene-Bis-(4-Hydroxycoumarin) or Dicumarol on Prothrombin and Coagulation Times of Blood; Preliminary Report, Cleveland Clin. Quart. **9**: 147, 1942.
21. Lehmann, J.: Hypoprothrombinemia Produced by Methylene-Bis-(Hydroxycoumarin), Lancet **1**: 318, 1942.
22. Bollman, J. L., and Preston, F. W.: The Effects of Experimental Administration of Dicoumarin, J. A. M. A. **120**: 1021, 1942.
23. Dale, D. U., and Jaques, L. B.: The Prevention of Experimental Thrombosis by Dicoumarin, Canad. M. A. J. **46**: 546, 1942.
24. Richards, R. K., and Cortell, R.: Studies on the Anticoagulant 3,3′-Methylene-Bis-(4-Hydroxycoumarin), Proc. Soc. Exper. Biol. & Med. **50**: 237, 1942.
25. Shapiro, S., Redish, M. H., and Campbell, H. A.: Studies on Prothrombin. II. The Effects of a Single Small Dose of Dicumarol (3,3′Methylenebis [4-Hydroxycoumarin]), Am. J. M. Sc. **205**: 808, 1943.
26. Evans, J. A.: The Combined Use of Heparin and Dicoumarin (3,3′-Methylene-bis-4-Hydroxycoumarin) in Thrombophlebitis and Pulmonary Embolism (Preliminary Report), Lahey Clin. Bull. **2**: 248, 1942.
27. Stats, D., and Bullowa, J. G. M.: Effect of a Single Dose of 3,3′-Methylene-Bis-(4-Hydroxycoumarin) on Blood Coagulation in Humans, Proc. Soc. Exper. Biol. & Med. **50**: 66, 1942.

ALTERATIONS IN THE FORM OF THE T WAVES WITH CHANGES IN HEART RATE

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ALTERATIONS of the ventricular electrocardiogram appear occasionally in the first normal beat which follows an extrasystole. When a conduction disturbance exists in one of the bundle branches, the long postextrasystolic pause may permit better recovery of the specific tissue, thus improving the conduction of the first postextrasystolic beat. The signs of intraventricular block may disappear from this ventricular complex in the electrocardiogram.[5, 16] Variations of the first postextrasystolic T wave are also encountered after interpolated ventricular extrasystoles; the recovery time for the first postextrasystolic beat is too short, and the stimulus for the first ventricular contraction after the extrasystole spreads aberrantly within the ventricles. In such instances, changes are usually also seen in the QRS complex. Finally, after a long series of extrasystoles (paroxysmal tachycardia), T-wave changes may be found for a short time;[3] they can be explained by the cardiac damage caused by the tachycardia (anoxia, exhaustion).

This paper deals with alterations of the T waves and of the S-T segments which appear in the first postextrasystolic beat after single extrasystoles and without changes of the QRS complex. Hitherto they have rarely been observed, and have not, to our knowledge, received detailed study.

Electrocardiograms made at the Metropolitan Hospital during the years 1940 to 1942 constituted the material used in this investigation. In these three years, 16,810 tracings were taken. Occasionally more than one electrocardiogram was made on the same patient. In the Medical Department, an electrocardiogram was recorded routinely on every patient; in the other departments this happened only if an arrhythmia was discovered or a heart lesion suspected. The number of older patients in this hospital population is somewhat higher than in most general hospitals.

Extrasystoles were found in 168 cases, that is, in one per cent of the electrocardiograms taken. Changes in the final deflection of the first postextrasystolic beat were seen in 57 cases, or one-third of those with extrasystoles. Among these 57 patients, 14 had auricular, and 43 ventricular, extrasystoles. In 15 cases, the electrocardiogram was otherwise normal, or showed only left axis deviation. In the others the changes varied. The pattern of left ventricular strain (left axis devia-

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tion with displacement of S-T segment and T waves in a direction opposite to the main deflection) was seen frequently. Some patients showed the classical pattern of anterior wall infarction, others had inverted T waves in Lead I or II, and a few showed widening or splitting of the QRS complexes.

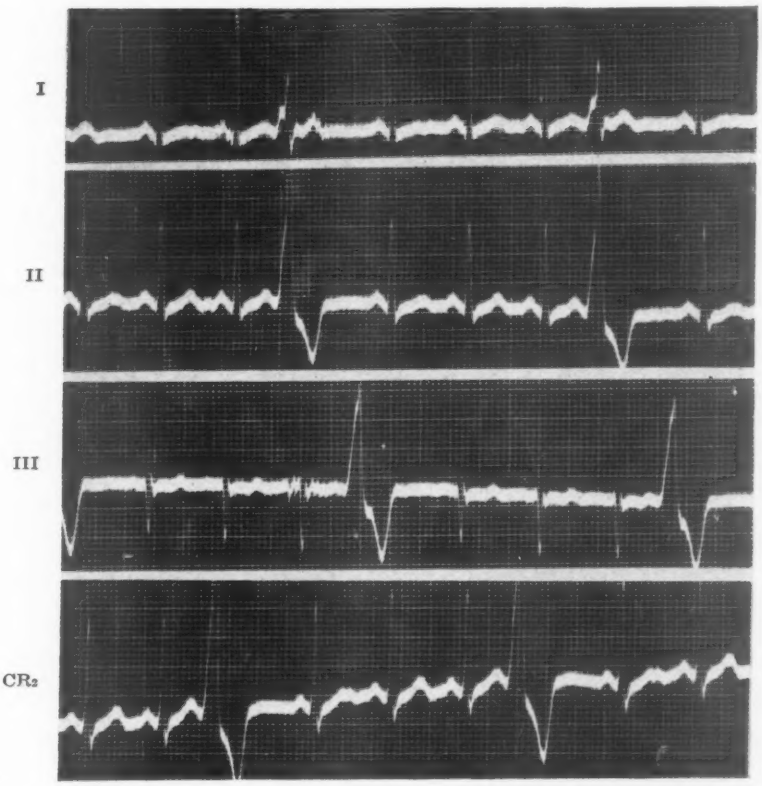

Fig. 1.—Ventricular extrasystoles in a case of left axis deviation; there are changes in the form of the T wave in the first postextrasystolic beat.

Some of the data collected from the 57 patients with changes in the T waves of the first postextrasystolic beat are shown in Table I. The first column gives the number; the second, the age of the patient; the third states the type of extrasystoles found; and the fourth indicates in which lead a postextrasystolic beat was registered. (Since all of the tracings were routine electrocardiograms, extrasystoles were frequently not registered in all leads.) The fifth column notes the presence or absence of evidence of organic heart disease, and the chief electrocardiographic findings are mentioned in the sixth. In the seventh column the changes in the T waves of the first postextrasystolic beat are described.

Fig. 1 was taken from a 32-year-old patient with hypertension (Case 50 of Table I). The electrocardiogram shows sinus tachycardia, with a

TABLE I

NUMBER	AGE (YR.)	TYPE OF EXTRASYSTOLES	LEAD IN WHICH POST-EXTRASYSTOLIC T WAVES WERE VISIBLE				PRESENCE OF ORGANIC HEART DISEASE	CHIEF FINDINGS IN THE ELECTROCARDIOGRAM	TYPE OF CHANGES IN THE POST-EXTRASYSTOLIC T WAVES
			I	II	III	C			
1	55	Ventricular	+	+	+	0	No	Left axis deviation	Positive T waves in Leads I and II are higher; negative T in Lead III is more negative
2	42	Ventricular	+	+	+	+	Yes	Left ventricular strain	No changes in limb leads; positive T in chest lead is diphasic
3	56	Auricular	+	+	+	+	Yes	Marked changes in QRS complex and T waves	Negative T in Leads I and II is more negative, positive T in Lead III is higher, positive T in chest lead is deep negative
4	73	Auricular	+	+	+	+	Yes	Left axis deviation, prolonged P-R	Positive T in Lead I is higher, negative T in Lead III is more negative
5	52	Ventricular	0	+	0	0	Yes	Anterior wall infarction	Positive T in Lead II is lower
6	36	Auricular	+	+	+	0	Yes	Anterior wall infarction	Flat T in Leads II and III becomes higher
7	72	Auricular	+	+	0	+	Yes	Left ventricular strain	Negative T in Lead I is positive, low T in Lead II is higher, positive T in chest lead is much higher
8	35	Ventricular	0	0	0	+	Yes	Normal	Positive T in chest lead is lower
9	61	Auricular	0	+	0	0	No	Normal	Positive T in Lead II is higher
10	56	Ventricular	0	+	+	0	Yes	Left ventricular strain	Negative T in Leads II and III becomes much more negative
11	71	Ventricular	+	+	+	+	Yes	Left ventricular strain	Negative T in Leads II and III is less negative; positive T in chest lead is lower
12	38	Ventricular	0	0	+	0	Yes	Anterior wall infarction	Negative T in Lead III is less negative
13	82	Auricular	+	+	+	+	Yes	Posterior wall infarction	Negative T in chest lead is positive
14	80	Ventricular	+	+	+	+	Yes	Left ventricular strain	Positive T in chest lead is negative

15	80	Ventricular	+	+	+	+	Yes	Left ventricular strain	Negative T in Lead I is positive, positive T in Lead III is negative, positive T in chest lead is lower
16	79	Ventricular	0	+	0	0	Yes	Left ventricular strain	Flat T in Lead II is negative
17	60	Ventricular	+	+	+	+	No	Left axis deviation	Positive T in Leads I and II is lower, negative T in Lead III is positive, positive T in chest lead is lower
18	60	Ventricular	+	+	+	+	No	Left axis deviation	Positive T in Leads II and III is lower
19	62	Ventricular	0	+	0	0	Yes	No T in Lead I	Positive T in Lead II is much lower
20	80	Ventricular	0	0	+	+	Yes	Negative T in Leads I and II	Negative T in Lead III is positive, positive T in chest lead is lower
21	8	Auricular	+	+	+	+	No	Normal	Positive T in Leads I and II is higher, diphasic T in chest lead is negative
22	66	Ventricular	+	+	+	+	Yes	Abnormal T in Leads I and II	Very low T in Leads I and II becomes negative, positive T in chest lead is lower
23	45	Ventricular	+	+	+	+	Yes	Normal	Positive T in Lead I is negative, negative T in Lead III is positive
24	46	Ventricular	+	+	+	+	Yes	Abnormal QRS complexes and T waves	S-T depression is more marked and positive T in Lead II is lower
25	67	Ventricular	+	0	0	0	Yes	Left axis deviation, low T in Lead I	Low T in Lead I is negative
26	52	Ventricular	0	0	0	+	Yes	Marked changes	Positive T in chest lead is much higher
27	75	Auricular	+	+	+	+	Yes	Left ventricular strain	Negative T in Lead I is positive, positive T in Lead III is negative, positive T in chest lead is higher
28	56	Ventricular	+	+	+	+	Yes	Left ventricular strain	Depression of S-T in Lead I disappears, positive T in Leads I and II is lower
29	56	Ventricular	+	0	+	+	Yes	Left ventricular strain	Negative T in Lead I is deeper, positive T in Lead III is higher
30	38	Ventricular	+	+	+	0	Yes	Low T in Lead I, no T in Lead II	Low T in Lead I disappears, T in Leads II and III is negative

TABLE I—CONT'D

NUMBER	AGE (YR.)	TYPE OF EXTRASYSTOLES	LEAD IN WHICH POST-EXTRASYSTOLIC T WAVES WERE VISIBLE				PRESENCE OF ORGANIC HEART DISEASE	CHIEF FINDINGS IN THE ELECTROCARDIOGRAM	TYPE OF CHANGES IN THE POST-EXTRASYSTOLIC T WAVES
			I	II	III	C			
31	52	Ventricular	+	+	+	0	Yes	Normal	Positive T in Leads I and II is lower, negative T in Lead III is less negative
32	66	Ventricular	+	0	+	0	Yes	Left ventricular strain	Negative T in Lead I is low positive
33	89	Ventricular	+	0	0	0	Yes	Left axis deviation	Positive T in Lead I is higher
34	71	Auricular	+	+	+	0	Yes	Left ventricular strain	T in Leads II and III is lower
35	69	Ventricular	+	+	+	+	Yes	Left ventricular strain	Negative T in Lead I is less negative, positive T in Lead II is negative, positive T in Lead III is much lower, positive T in chest lead is negative
36	84	Ventricular	0	+	+	0	Yes	Normal	Positive T in Leads II and III is lower
37	52	Auricular	+	+	+	+	Yes	Negative T in each lead	Negative T in Lead I is less negative, T in Lead II is invisible, negative T in Lead III is less negative, negative T in chest is positive
38	65	Auricular	+	+	+	0	Yes	Normal	Positive T in Lead I is lower, negative T in Lead III is higher
39	73	Ventricular	+	+	+	+	Yes	Left ventricular strain	S-T segment in Leads I and II is more depressed
40	48	Ventricular	+	+	0	0	Yes	Low T waves	T in Leads I and II is higher
41	52	Ventricular	+	+	+	0	Yes	Normal	Positive T in Leads I and II is higher, positive T in Lead III is negative
42	65	Ventricular	0	0	+	+	Yes	Normal	T in Lead III and chest lead is lower
43	29	Ventricular	+	+	+	+	Yes	Abnormal T waves	Negative T in Lead II becomes positive, positive T in Lead III is higher, negative T in chest lead is more negative
44	83	Auricular	+	+	+	+	Yes	Left ventricular strain	Negative T in Leads I and II is less negative, T in Lead III is higher, positive T in chest lead is higher

45	78	Ventricular	+	+	+	0	Yes	Normal	Positive T in Leads I and II is lower, negative T in Lead III is more negative
46	63	Auricular	+	+	+	+	Yes	Left ventricular strain	Depressed S-T in Lead I is higher
47	46	Ventricular	+	+	+	0	Yes	Low T in Lead I	T in Leads I and II is lower
48	38	Ventricular	+	0	+	0	Yes	Negative T in Leads I and II	Negative T in Lead I is less negative, positive T in Lead III is lower
49	54	Ventricular	0	+	0	+	No	Normal	Positive T in Lead II is much higher, positive T in chest lead is lower
50	32	Ventricular	+	+	+	+	Yes	Left axis deviation low T in Lead I	Positive T in Lead I is isoelectric, positive T in Lead III is higher, positive T in chest lead is lower
51	70	Auricular	+	+	+	0	Yes	Abnormal T waves	Positive T in Lead I is negative, positive T in Lead III is higher
52	62	Ventricular	0	+	+	0	Yes	Low T in Lead I	Positive T in Leads II and III is higher
53	68	Ventricular	+	+	+	0	Yes	Left ventricular strain	Low T in Lead I is positive, positive T in Lead II is higher, positive T in Lead III is negative
54	57	Ventricular	+	+	0	+	Yes	Left ventricular strain	Positive T in Lead I is lower, positive T in chest lead is lower
55	60	Ventricular	+	+	+	0	Yes	Left ventricular strain	Low T in Leads I, II and III becomes lower
56	71	Ventricular	0	0	0	+	Yes	Negative T waves	Negative T in chest lead is positive
57	41	Ventricular	+	+	+	0	Yes	Normal	Positive T in Lead I is lower, positive T in Lead III is higher

heart rate of 110 and left axis deviation, without other changes in the QRS complexes. The T waves are positive in each lead, but rather low in Lead I. A ventricular extrasystole appears after every second or third beat. In Lead I the T waves of the first postextrasystolic beat become lower and slightly diphasic. The T wave in Lead II also becomes flattened after the extrasystole; in Lead III it is higher for the one beat after the extrasystole, and, in Lead CR_2, the changes are similar to those in Lead I.

Fig. 2 shows five tracings from five different patients. The first tracing, *A*, is Lead I, taken from a patient who suffered from coronary sclerosis; the T waves were inverted in all leads. The T wave in this tracing (Fig. 2) becomes positive in the first beat after the ventricular extrasystole. The same alteration may be seen in the second tracing, *B*, which is from a 54-year-old patient with coronary sclerosis; Lead II is reproduced. In this case the extrasystoles appear so late that the postextrasystolic pause is no longer than the normal pause. In the third tracing (Fig. 2, *C*), Lead III is reproduced; there were no T waves in any lead. An inverted T wave appears, however, immediately after a ventricular extrasystole. The first ventricular complex of this tracing also follows an extrasystole, and has, therefore, an inverted T wave. The fourth tracing, *D*, shows inverted T waves in the chest lead (CR_2) of a 63-year-old patient with coronary sclerosis; the T wave of the first postextrasystolic normal beat becomes positive. The fifth tracing, *E* (CR_2), from a 52-year-old patient with coronary sclerosis, shows deep, negative T waves. After an auricular extrasystole whose P wave is buried in the preceding T wave, the T wave of the first postextrasystolic sinus beat is less negative, and is followed by a positive component. The first complex of this tracing shows the same thing because it succeeded an auricular extrasystole.

Similar alterations were observed in other cases. Positive T waves were higher or lower in the first postextrasystolic beat, and inverted T waves more, or sometimes less, inverted; positive T waves became negative, and vice versa. Sometimes the changes were found in all leads, in other cases in only two. Occasionally they were visible only in the chest lead. At times, an inverted T wave in Lead I became positive, whereas a positive T_3 became negative. No changes in the QRS complex of the first postextrasystolic beat were observed. Both auricular and ventricular extrasystoles were present in some cases. The T-wave changes were identical after both types of extrasystoles.

Even when definite electrocardiographic patterns existed, the type of change in the T wave of the first postextrasystolic beat could not be predicted. In 19 cases of hypertension, the pattern of left ventricular strain was found; in 9 of these cases the S-T segment of the first postextrasystolic beat was less depressed and the T waves became positive. In 4 instances, however, the negative T wave in Lead I became more negative, whereas, in 6, there were no changes in the T wave in this

lead. The T waves of the chest lead also showed different changes in individual cases. In 9 cases in which there were definite evidence of myocardial involvement and a low or inverted T wave in Lead I, this became either higher or positive after the extrasystoles. In 5 cases in which the electrocardiogram was normal, the positive T wave in Lead I became inverted after an extrasystole. These five patients had cardiovascular disease (hypertension, angina pectoris, coronary sclerosis).

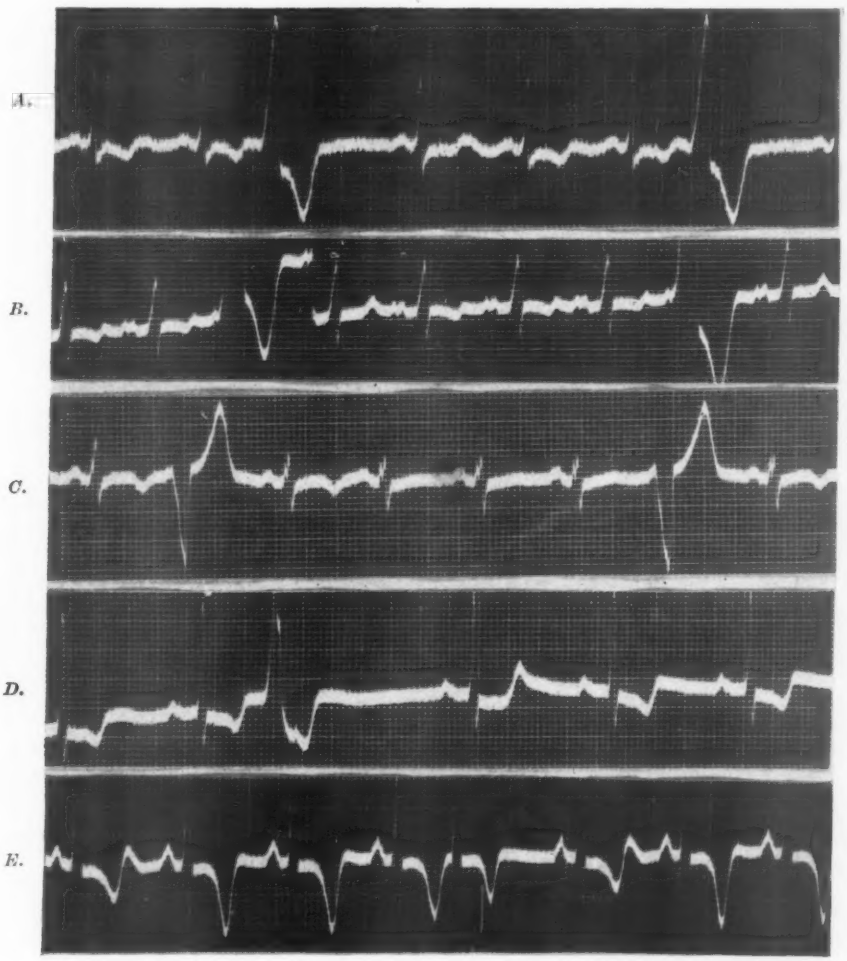

Fig. 2.—Changes in the T waves of the postextrasystolic beats in five cases.

Reference was made earlier to 16 cases in which the electrocardio gram showed no signs of myocardial damage. Other observations indicated, however, the presence of organic heart disease in 9 of these cases. Therefore, there were only 7 patients without definite proof of an organic heart lesion. Since some were over 50 years of age, coronary

sclerosis was possibly present. In 4 of the 7 cases, the T wave became higher after an extrasystole. In the remaining 3 it became lower or inverted. One of these patients (Case 17 of Table I), a 60-year-old man, had a thyroid adenoma; in the other 2 (Cases 18 and 31), who were 60 and 52 years old, respectively, no proof of organic heart disease was found. The patients, however, were not observed sufficiently long to exclude an organic heart disease such as coronary sclerosis. Accordingly, in only three of 57 cases did the electrocardiogram of the first beat after the extrasystole show an alteration of the T wave in the sense of a myocardial lesion (lowering or inversion of the T wave) when there was no decisive evidence for the existence of heart disease.

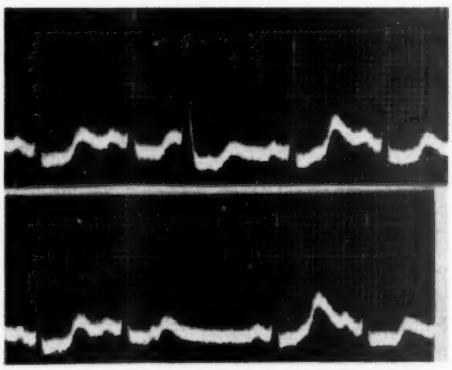

Fig. 3.—The upper tracing shows changes in the postextrasystolic T wave after a conducted auricular extrasystole; the lower shows the same changes after a blocked auricular extrasystole.

These observations seem to warrant the conclusion that the T-wave changes in the first postextrasystolic beat are not rare. A normal or abnormal T wave may become more positive or more negative. Up to the present no definite rules could be drawn which were reliable for all types of changes. It can be said, however, that a change in the T wave in Leads I and II in the direction of negativity, and indicative of an abnormal electrocardiogram, is very rare when the heart is healthy, presuming that it occurs at all.

The changes in the T wave of the first postextrasystolic beat might be ascribed to the extrasystole or to the long pause which follows it.

Tracings like those in Fig. 3 show that the long diastole which follows an extrasystole, and not the extra contraction itself, may cause changes in the final deflection of the first postextrasystolic beat. Auricular extrasystoles, many of which were blocked, and sinus tachycardia with 100 beats per minute were present in this case. The S-T segment was depressed and the T waves were positive. In the upper tracing, two normal beats are followed by an extrasystole. Its origin cannot be ascertained with certainty from this tracing. Since the postextrasystolic pause is not compensatory, and many other tracings from this patient

in other leads showed only auricular extrasystoles, an aberrant auricular extrasystole may be assumed also in this tracing. The normal beat after the extrasystole has a much higher T wave. In the lower tracing, from the same patient, one sees a blocked auricular extrasystole. The normal beat which follows shows the same changes as the postextrasystolic beat in the upper tracing, in spite of the fact that there was no premature ventricular contraction. In another case, both conducted and blocked auricular extrasystoles were followed by the same lowering of the T waves of the first postextrasystolic beat.

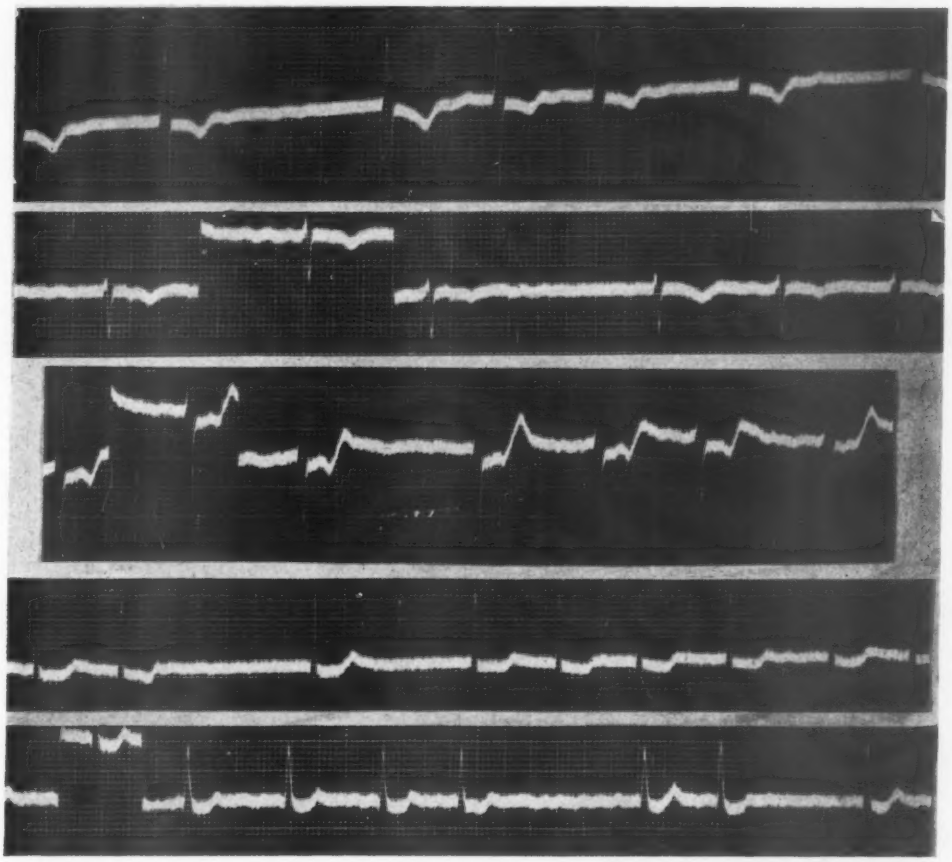

Fig. 4.—Five tracings from patients with auricular fibrillation; the form of the T wave changes with the length of the preceding diastole.

Likewise, it became clear from observations on other arrhythmias that a premature ventricular contraction is not a prerequisite for the changes in the T wave.

In Fig. 4, tracings are reproduced which were taken from five patients who suffered from coronary selerosis and auricular fibrillation. The first tracing (Lead III) shows clearly that the T waves become in-

creasingly negative as the preceding pause lengthens. The same changes are visible in the second tracing (Lead CR_2). In the third tracing (Lead CR_2), however, the T waves are higher after a longer diastole, and the same situation appears in the fourth and fifth tracings (Lead I). No change in the QRS complex accompanies these alterations of the T waves. In the three-year period during which the tracings were examined in regard to the postextrasystolic T-wave changes, variform T waves, as in Fig. 4, were noted in 22 cases of auricular fibrillation. Since auricular fibrillation was observed in several hundred cases, this phenomenon may be considered uncommon, but by no means rare. In only 5 of these 22 cases was there lowering or inversion of the T waves after a longer pause. In 17 instances they became higher when the preceding diastoles were longer. The type of change varied in different leads from the same patient. Sometimes, after a longer pause, the T wave in Lead I became higher, whereas, in Lead III, it became lower. Occasionally, variations appeared in only one of the limb leads or only in the chest lead. Changes in the T waves in all 22 cases were more pronounced as the length of the preceding diastole increased.

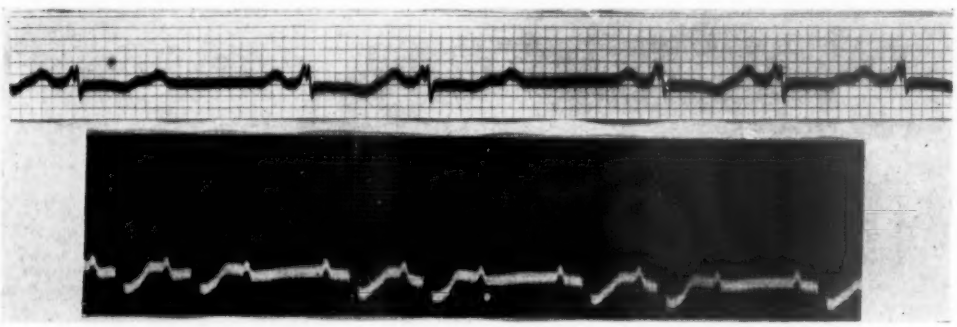

Fig. 5.—Changes in the form of the S-T segment and T wave in two cases of partial heart block after diastoles of different length.

Fig. 5 shows two tracings from patients with disturbances of auriculoventricular conduction and blocked auricular beats, causing the periodic appearance of longer pauses. The T wave of the systole after a longer pause is altered in both tracings. In the upper tracing (Lead I), partial auriculoventricular block (3:2 and 4:3) existed with a constant P-R interval. The T wave of the ventricular complex which follows a longer pause due to the blocking of an auricular stimulus is always deeper than the other T waves. Continuous 3:2 block, with fixed length of the P-R interval, is present in the second tracing. Here again, the S-T segment of the beat after the longer pause always differed from that of the other beats in that it had a much straighter course.

The tracings presented thus far show changes in the S-T segments and T waves alone. If alterations also appear in the QRS complexes, another mechanism should be considered. Fig. 6 shows distinct changes in the QRS complex and in the final deflections of the beats which

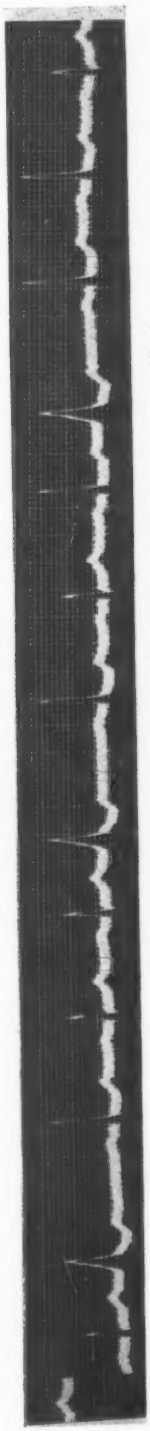

Fig. 6.—A case of ventricular extrasystoles and varying intraventricular block.

follow the first two extrasystoles. One sees, however, the same deviations before the third extrasystole and also in the second beat following it. The same changes appeared in other tracings from the same patient, at times without extrasystoles. We may, therefore, assume that the changed form of the postextrasystolic beat in this case was due to an intraventricular disturbance of conductivity.

DISCUSSION

Changes in the T waves after extrasystoles have been noted before. They are frequently to be found in experimental or clinical tracings in textbooks or articles, without remarks by the authors.

To the best of our knowledge, White was the first to notice changes in the postextrasystolic T waves. He described them in a paper on the alternating pulse as "slight alternation of the T-deflection" after premature beats. All of his patients had organic heart disease; tracings obtained from two patients were reproduced. They show deep inversion of the T wave for one beat after the extrasystole.

Baeq described the same phenomenon as "periodic change of the T wave" in hypertensives. In one case the positive T wave became negative after an extrasystole. A similar case was reported by Laubry and Poumailloux as an example of "electric alternans." This patient also had hypertension. The positive T wave was inverted after the extrasystole, the next T was again positive, the following one was negative, and then the T waves remained positive. No attempt is made by these authors to explain the changes in the postextrasystolic T waves.

Von Kapff reported one case in 1930 and 7 more in 1932. Evidence of organic heart disease was available in 6 out of these 7 cases. Among 8 cases published by von Fernbach, 6 patients had signs of heart disease and 7 had cardiac symptoms. T-wave alterations after extrasystoles have also been described experimentally.[2, 12] The T-wave changes in other arrhythmias do not seem to have received attention before.

In order to explain these changes, the following possibilities are worth consideration.

1. *The Altered Form of the T Wave of the First Postextrasystolic Beat is Due to a Change in Intraventricular Conduction.*—A disturbance of intraventricular conductivity may appear or become more pronounced if the diastole is too short and the recovery from the preceding systole is insufficient; this may happen with extrasystoles because the specific tissue conducts twice within a short time, and the postextrasystolic pause may be inadequate to permit full recovery. On the other hand, an intraventricular disturbance of conductivity may be diminished if a beat follows a longer diastole, which permits better recovery. It is known experimentally and clinically that intraventricular conduction disturbances may cause marked changes in the T waves.[14] However, it is the rule that, in such cases, some change in the form of the QRS complex appears (Fig. 6), even if this change consists

merely in the height of a single wave. Since in all the cases collected in this paper there were marked alterations in the final deflection without any change in the initial complex, one cannot attribute the phenomenon to abnormal intraventricular conduction of the first postextrasystolic beat.

2. *The Abnormality in the Size and Shape of the Heart Due to the Increased Filling in the Long Postextrasystolic Diastole Is the Cause of the T-Wave Changes.*—The augmented filling of the ventricles after an extrasystole, which is clearly visible under the fluoroscope and in the kymograph, causes enlargement of the heart, thereby increasing its area of contact with neighboring tissues of good conductivity. The extent of this contact influences the electrocardiogram markedly. For currents of injury it has been established that prevention of direct contact between an injured area and the diaphragm abolishes the admixture of these currents to the electrocardiogram in the limb leads, and that the high take-off in the electrocardiogram reappears as soon as this contact is re-established.[8, 12] Changes in the T waves of normal persons which depend upon change in posture have also been explained as the result of a difference in the contacts between the heart and the neighboring muscle mass.[13, 15] Since, however, the T wave is registered during the height of the ventricular contraction, it may be assumed that the size and position of the heart at this period are the same for all beats, irrespective of the size of the organ during diastole, providing the heart is normal and empties completely. Under abnormal conditions an incomplete systolic emptying of the heart is possible if cardiac filling in the postextrasystolic diastole is increased. Since the changes in the T waves described earlier usually appear when the heart is abnormal, this possibility cannot be completely discarded.

3. *The Changes in the T Wave Appear in Connection With an Alteration in the Force of the Systolic Contraction of the First Postextrasystolic Beat Caused by the Extrasystole.*—The postextrasystolic contraction is stronger for two reasons: (a) the greater filling of the heart in the long postextrasystolic pause (discussed under heading *5*); (b) the "strengthening" effect of the extra contraction on the following beat. Any single contraction which follows another after a short interval increases the height of the next systole.[11, 18] This strengthening effect becomes greater, as the interval between the two contractions becomes shorter. Woodworth has studied this effect on the perfused apex or base of the dog's ventricle. It was confirmed by Rihl on the perfused heart, in situ, under more natural conditions. This phenomenon depends solely on the prematurity of the preceding beat; it may be found even if the postextrasystolic pause is equal to a normal period. It is not always present in experiments on the intact animal because other factors, like changes in ventricular filling, may interfere. Observations, similar to those in Figs. 3, 4, and 5, show, however, that changes in the length of diastole, but not premature contractions, are prerequisites for the alterations in the T waves.

4. *The T-Wave Changes After Extrasystoles Might be Attributed to an Alteration in the Cardiac Blood Supply or Nutrition Caused by the Extrasystole.*[4, 7]—Alteration in the blood supply, or "nutrition," as a consequence of the extrasystoles would not become manifest so quickly nor would it be limited to a single beat. The fact that the same changes in the T wave appeared also in arrhythmias without extrasystoles, moreover, militates against these explanations.

5. *The Changes in the T Waves are Connected With a Change in the Filling of the Heart.*—This possibility was discussed, but discarded, by Kapff. Variations in filling must be assumed to exist in all conditions in which the changes in the T waves described in this paper appear. The stroke volume of the postextrasystolic beat is increased approximately by the amount of blood not moved by the extrasystole, that is, occasionally by as much as 100 per cent. The stroke volume may also be doubled in heart block. Increased filling causes a stronger systole. Whether this, in turn, changes the T wave is a disputed question. According to Pardee, the form of the T wave seems to be influenced by the strength of the contraction; the T wave is larger in athletes and smaller after acute diseases. The different metabolic processes accompanying alteration of contractility seem to be the most probable explanation for the changes in the T waves as described. It is conceivable that changes in the strength of systole are unaccompanied by changes in the form of the T wave under normal conditions, but appear if the heart is in some way "damaged."

Although definite proof for any of these explanations is lacking, those mentioned under headings *1*, *3*, and *4* seem rather improbable. The observations described in this paper show that the postextrasystolic changes in the T waves do not depend on the preceding premature ventricular systole; they appear in connection with the preceding longer pause.

Tracings similar to the second in Fig. 2, in which marked T-wave changes appeared even when the postextrasystolic pause was not longer than the other diastoles, speak against the importance of the length of the pause alone, without changes in the filling of the heart.

Any change in the T wave of the first postextrasystolic beat in the direction of abnormality (lowering or inversion of the T waves in Leads I and II) seems to speak in favor of existing heart disease, because such changes were found only three times in patients without organic heart disease, whereas the number of cases in which no changes in the T waves appear after extrasystoles or during auricular fibrillation is very large.

Almost every third patient reported in this study showed some change in the T wave of the postextrasystolic beat. This is certainly due to the fact that the number of patients with extrasystoles and a normal heart was small in the hospital material. It is noteworthy that, as far as we know, in cases with a marked respiratory arrhythmia, in which, sometimes, very pronounced changes in the length of the diastole

appear, T-wave changes have not been described as yet. Such hearts are usually healthy or not profoundly damaged. Moreover, these changes were not seen in many hundred cases of partial heart block observed personally; the two tracings in Fig. 5 were a rare exception.

From the fact that marked changes in the T waves appear in some arrhythmias, depending exclusively on the length of the diastole, we may infer that, in some cases without arrhythmias, a change in the rate alone, without any intrinsic change in the heart, may cause alterations in the form of the T waves.

CONCLUSIONS

Alterations in the form of the T waves of the first postextrasystolic beat are described and analyzed. These changes are not rare. They are also found after blocked auricular extrasystoles and after long diastoles in auricular fibrillation and heart block.

Lowering or inversion of the T waves in Leads I and II after a long diastole seems to indicate the presence of myocardial damage. Changes in the form of the T waves in cases of myocardial damage may be due to a change in rate only.

The mechanism leading to these alterations in the T waves has been analyzed; they seem to be chiefly connected with changes in the filling of the heart.

REFERENCES

1. Bacq, F. M.: Des variations rythmiques d'electrocardiogramme dans les etats hypertensifs, Arch. internat. de méd. exper. **5**: 55, 1929.
2. de Boer, S.: Die physiologische Grundlage und Klinik des unregelmaessigen Herzschlages, Ergebn. d. inn. Med. u. Kinderh. **29**: 391, 1926.
3. Burak, M., and Scherf, D.: Angina Pectoris und paroxysmale Tachykardie, Wien. Arch. f. inn. Med. **23**: 475, 1933.
4. Fernbach, J.: Die Veraenderungen des Elektrokardiogramms nach Kammerextrasystolen, Deutsches Arch. f. klin. Med. **177**: 59, 1934.
5. von Kapff, W.: Ueber einen Fall von passagerem Schenkelblock, Klin. Wchnschr. **7**: 357, 1928.
6. von Kapff, W.: Ueber postextrasystolische Aenderung der T-Zacke, Ztschr. f. Kreislaufforsch. **24**: 273, 1932.
7. Katz, L. N.: Electrocardiography, Philadelphia, 1941, Lea & Febiger.
8. Katz, L. N., Gutman, I., and Ocko, F. H.: Alterations in Electrical Field Produced by Changes in Contacts of Heart With Body, Am. J. Physiol. **116**: 302, 1936.
9. Laubry, C., and Poumailloux, M.: L'alternance èlectrique, Arch. d. mal. du coeur **23**: 456, 1930.
10. Pardee, H. E. B.: Clinical Aspects of the Electrocardiogram, ed. 4, New York, 1941, Paul B. Hoeber, Inc.
11. Rihl, J.: Zur Erklaerung der Vergroesserung der postextrasystolischen Systole des Saeugethierherzens, Ztschr. f. exper. Path. u. Therap. **3**: 1, 1906.
12. Scherf, D.: La conduccion de las corrientes de injuria desde el corazon, Rev. argent. de cardiol. **8**: 87, 1941.
13. Scherf, D., and Weissberg, J.: The Alterations of the T Waves Caused by a Change of Posture, Am. J. M. Sc. **201**: 693, 1941.
14. Scherf, D., and Boyd, L. J.: Clinical Electrocardiography, St. Louis, 1940, The C. V. Mosby Co.
15. Sigler, L. H.: Electrocardiographic Changes Occurring With Alterations of Posture From Recumbent to Standing Positions, Am. Heart J. **15**: 146, 1938.
16. Stenstroem, N.: Further Experience on Incomplete Bundle Branch Block in Man, Acta med. Scandinav. **67**: 353, 1927.
17. White, P. D.: Alternation of the Pulse; a Common Clinical Condition, Am. J. M. Sc. **150**: 82, 1915.
18. Woodworth, R. S.: Maximal Contraction, "Staircase" Contraction, Refractory Period, and Compensatory Pause of the Heart, Am. J. Physiol. **8**: 213, 1902.

MORPHOLOGIC STUDY OF THE CARDIAC CONDUCTION SYSTEM

PART III: BUNDLE BRANCH BLOCK

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THE bundle branch block concept appears to have originated in the mind of Rothberger. In 1909, he and Eppinger[1] were investigating the effect upon the electrocardiogram of local injury to the myocardium of the dog. They injected a silver nitrate solution into various localities of the heart wall and observed that, occasionally, even minute quantities produced immediate alteration in the ventricular curves and marked physiologic changes in the injured ventricle. When such changes took place, Rothberger suspected that the solution had entered one of the main branches of the His bundle and had produced bundle branch block.

Since two of us[2] have recently reported our inability to find a special muscular conducting bundle in either man or dog, we determined to analyze the information which has accumulated since the early observations of Rothberger and Eppinger. Our purpose was to learn whether the available evidence justifies the belief that the so-called bundle branch block complexes, obtained from experimental animals and man, are really due to blocking lesions in the branches of a special conducting system. In this communication, we present our analysis and our conclusions.

Eppinger and Rothberger[3] (1910) planned experiments to verify the theory which developed from their previous observations. With specially constructed knives, they entered the cavities of both lower chambers of the canine heart and made transverse sections into the upper part of the interventricular septum on the right and left sides (Fig. 1, *A*), and considered that their incisions were successful when they were followed immediately by the broad ventricular complexes shown in Fig. 1, *B* and by a "nachhinken" (limping after) of the injured ventricle. When these two changes occurred, they believed that the right or the left branch of the His bundle had been completely severed. However, they did not state how they were able to recognize the branches, nor how they could microscopically distinguish the branches from the neighboring muscle elements. They offered no control observations to exclude the possibility that the electrocardiographic

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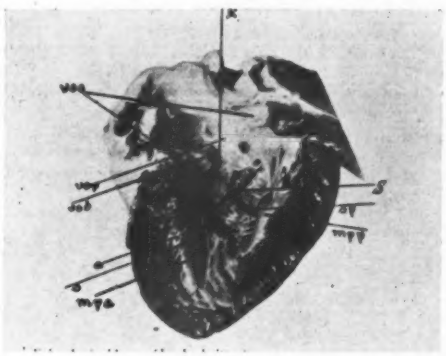
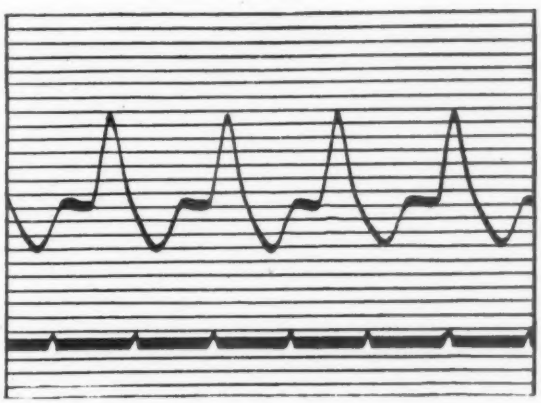
and structural changes were the result of experimental mutilation or of the severing of adjacent muscle fasciculi.

Independent of the Viennese investigators, Barker and Hirschfelder[4] had, in 1909, published their results after severing the left bundle branch, but they concluded that the muscle bundles described by Tawara had no special function.



A.

Fig. 1.



B.

Fig. 1.—The first experiment on bundle branch block. (Eppinger and Rothberger.) *A*, Incision of left septum. *B*, Resulting electrocardiogram—anoesophageal lead.

Rothberger and Winterberg[5] continued the experimental observations on bundle branch block in the dog, while Eppinger and Stoerck[6] searched for cases of bundle branch block in man, for by this time Einthoven's string galvanometer had been introduced into the clinic. Here, however, the three limb leads were employed, whereas Rothberger continued to rely on the anoesophageal lead. Since Lead III is somewhat analogous to the experimental anoesophageal lead, the clinical observers sought the diphasic, widened QRS complex in Lead III, and

considered that the form of the complex in Lead III determined not only the presence or absence of bundle branch block, but also the location of the blocking lesion.

When the right bundle branch was cut, Eppinger and Rothberger had obtained a ventricular complex like that of a left ventricular extrasystole. When, therefore, Eppinger and Stoerck found widened complexes in which the main spike was inverted in Lead III, they suspected that the right bundle branch had been blocked, and, when the main deflection was upright in the same lead, that the left had been interrupted. In two cases in which the complexes of right bundle branch block were traced (Fig. 2), necropsy was performed. In both, serial sections showed that the right branch was completely interrupted by fibrosis,

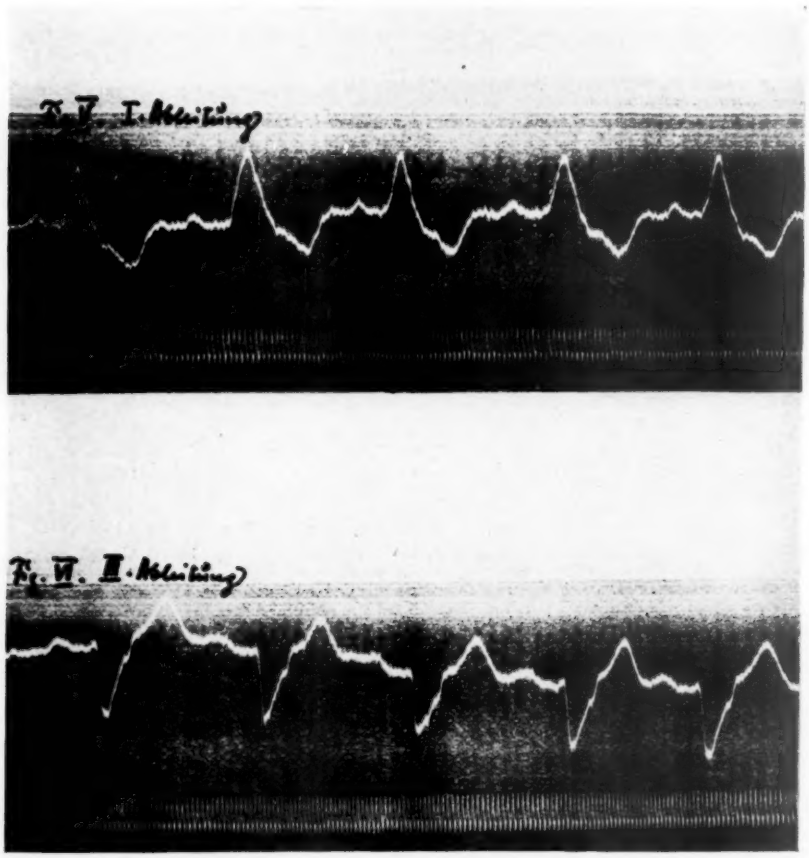


Fig. 2.—Right bundle branch block. (Eppinger and Stoerck.)

whereas the left branch was normal. The authors did not state how they distinguished the bundle branches from the ordinary myocardium. In their cases of right bundle branch block, Eppinger and Stoerck found the main ventricular deflection in Lead I directed oppositely to the main spike in Lead III.

This difference between the direction of the complexes in clinical and experimental bundle branch block disturbed Rothberger, who by this time was using Lead I as well as the anoesophageal lead in his experimental work on the dog. He and Winterberg found, after sectioning one branch, that the main initial ventricular deflections had the same direction in both leads. Consequently, they suspected that the block was not complete in the cases reported by Eppinger and Stoerck. They, therefore, undertook to produce partial block by cutting the posterior limb, the anterior limb, and the apical twigs of the left branch, and also the twigs from the right branch—individually and in various combinations. By these procedures, they were able to modify the ventricular complexes. Since the observations of Rothberger and Winterberg are startling, we give them in some detail.

1. The authors present a detailed, gross description of the main right and left branches of the His bundle, including their secondary branches. The illustrations, "drawings from nature," clearly show the posterior and anterior subdivisions, as well as the apical twigs of the left bundle branch; they show twigs given off from the right branch in the neighborhood of the septal papillary muscle; they do not show the junction of the branches and the stem.
2. They agree with Tawara that the bundle and its branches constitute a closed system.
3. They report:
   a. When only the anterior limb of the left branch was severed, no constant changes occurred. When only the posterior limb was cut, the R became taller and the S more shallow in the anoesophageal lead.
   b. When the left branch was intact, severing the right branch usually produced a left-sided extrasystole.
   c. The lengthening of the QRS interval, which always followed complete sectioning of the left branch, was not always noted after complete sectioning of the right.
   d. When the right branch was sectioned after *almost* complete severing of the left, complete A-V dissociation did not occur. (In one experiment complete heart block occurred after a cut limited to the posterior limb.)
   e. When the left branch was severed, the complexes of left bundle branch block were obtained, even though the right branch had previously been cut.
   f. Marked changes in the ventricular curves were often observed when the bundle branches were intact.
   g. Complete experimental right or left bundle branch block produced initial main deflections similarly directed in Lead I and in the anoesophageal lead.

Rothberger and Winterberg do not state how they distinguished conducting tissue from that of the ordinary myocardium. They surmised

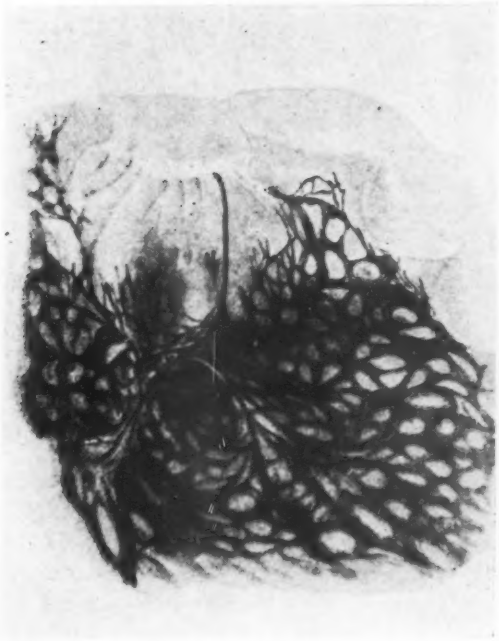
that, in the dog, as in man, not all of the pseudotendons contained Purkinje elements. They do not describe or show by illustration the junction of what they call the branches of the His bundle and the main stem. Nor do they account satisfactorily for the convenient appearance of a "tertiary center" after severing the left branch in animals whose right branch had already been sectioned.

While these studies were in progress in continental Europe, Lewis[7] and his associates in London were investigating experimental and clinical bundle branch block. Using dogs and one monkey, Lewis repeated the branch sectioning experiments of Rothberger and his associates. He found, like Rothberger and Winterberg, that, in most dogs when the right or left branch was cut, the initial ventricular complexes had the *same direction in all leads.* To such deflections, Lewis applied the term *concordant.* However, in some dogs and in the monkey, the initial deflections pointed oppositely to one another in Leads I and III. Such curves he called *discordant.* Lewis thought that discordant curves were caused by the paucity of pseudotendons in the hearts which traced them. In 1915, Lewis presented to the Royal Society the observations which he and Rothschild[8] had made on the spread of the excitation wave in the mammalian heart. Because of masterly diction and clear illustrations, these lectures made a deep impression on physiologists and cardiologists (Fig. 3).

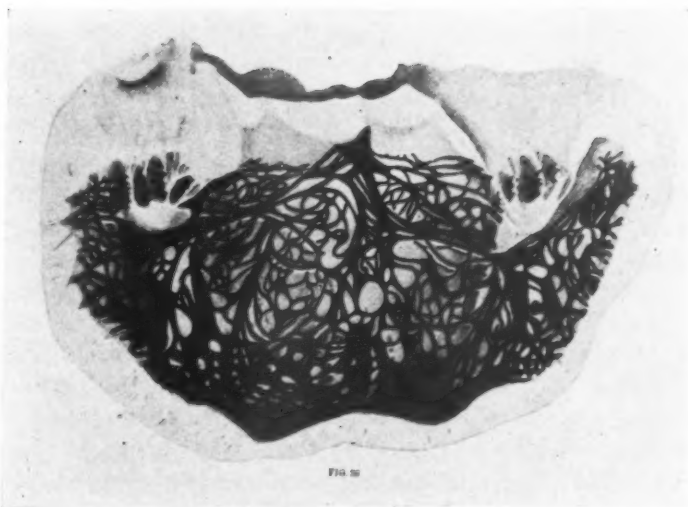
From their observations, Lewis and Rothschild concluded that the cardiac impulse travels through the His bundle approximately at the rate of 3,000 to 4,000 mm. per second, through the Purkinje network at the rate of 1,500 to 2,000 mm. per second, and through the myocardium at the more leisurely rate of 300 to 500 mm. per second. They explained the activation of the blocked ventricle as follows: the wave of excitation passes from the septal endocardium of the uninjured ventricle, through the septum, into the Purkinje network of the blocked ventricle, and thence into the ordinary myocardium. Only the eminence of Lewis and his masterly presentation can explain the general acceptance of this amazing theory.

We attempted, in vain, to bring to view a special conducting system in two canine hearts, according to the direction of Lewis and Rothschild; Barker, Macleod, and Alexander's[9] observations on the spread of the wave of excitation in mammals do not fully corroborate the findings of Lewis and Rothschild; Robb, et al.,[10, 11] found that the speed of the electrical impulse through the ventricular muscle was 2,375 ± 128 mm. per second, and also showed that Lewis, when he thought he had cut muscle bands crosswise, had actually made his cut parallel to the fibers. It is, therefore, apparent that there is need for a reinvestigation of the mode of activation of the mammalian ventricles.

While Lewis' experimental work was in progress, Carter[12] was searching the records of the London hospitals for electrocardiograms indicating bundle branch block. In 1914, he published a clinical study of



A.



B.

Fig. 3.—Drawings of canine ventricular conduction system, after staining with Best's alkaline carmine. (Lewis and Rothschild.) *A*, Right; *B*, Left.

twenty cases of right, and two cases of left, complete bundle branch block. The criteria he employed for the selection of his cases were the following:

1. Presence of P summits.
2. P-R interval frequently beyond 0.2 second.
3. QRS interval exceeds 0.1 second, and, as a rule, constitutes more than one-third of the entire ventricular complex.
4. Increased amplitude of initial deflection.
5. T, usually in the direction opposite to that of the prominent initial deflection, may be upright or inverted.
6. Initial deflection almost always shows notching in at least one lead; many bizarre forms seen.
7. T frequently much exaggerated.

The only evidence presented by Carter for the validity of his criteria was the microscopic observations in the two cases of Eppinger and Stoerck. However, the complexes in those cases do not show increased amplitude. It is not clear to us what other grounds Carter may have had for choosing his criteria, but it is apparent that he selected only cases in which there were curves that simulated preponderance deflections to represent complete right or left bundle branch block.

In the year that Carter published his clinical observations on bundle branch block, Cohn and Lewis[13] reported their pathologic study of four cases of bundle branch block (from serial sections). In one case, Cohn had difficulty tracing the right and left branches, but found a large amount of connective tissue involving the left branch. In another case, he found no lesion in the branches. In the third case, the stem and the branches were normal. In the fourth case, there were a slight increase of connective tissue in the stem and atrophy of fibrils in the left branch. Cohn and Lewis, therefore, concluded "that the cardiac conduction problem cannot be solved in the domain of pathologic anatomy."

From London, the interest in bundle branch block spread to the United States. Oppenheimer and Rothschild,[14] in 1917, published a study of sixty-two cases of intraventricular conduction defects. These cases clearly showed what a small percentage (6.4) of such defects actually fulfill Carter's criteria. Twenty-five of their patients had died; fourteen had come to necropsy. In eleven cases, microscopic serial sections were made, and, in eight of these, there was coronary arterial occlusion; in four, marked nodular sclerosis of the coronary arteries; and, in thirteen, marked patchy fibrosis of the myocardium, especially prominent in the endocardium and subendocardium of the left ventricle. From their observations, Oppenheimer and Rothschild concluded that atypical bundle branch block complexes were due to lesions involving the main branches of the His bundle, the twigs, and the Purkinje plexuses, and, therefore, named them *arborization block*. They stated that such complexes carried a poor prognosis.

The arborization block theory of Oppenheimer and Rothschild was accepted by some observers and rejected by others. For example, Carter[15] (1918) reported a clinical study of thirteen cases of arborization block, with a histopathologic study of one; and Willius[16] (1919) reported a clinical study of 138 cases of arborization block and also found that arborization block carried a poor prognosis. But Smith[17] doubted the arborization block explanation. From his own experiments with bundle branch block, he made the startling observation that severing a bundle branch was not in itself sufficient to produce a bundle branch block complex, and that such a complex was traced only after the injured ventricle had become dilated. Hence, Smith concluded that two factors, severing the branch and fatigue, were necessary for the production of the bundle branch block complex. Wilson and Herrmann[18, 19] (1920, 1921), in an analytical review and an experimental study of bundle branch block, concluded that the evidence presented by Oppenheimer and Rothschild did not sustain the arborization block theory.

Wilson and Herrmann were able, first, to construct complexes which varied from the normal biocardiogram to that of complete bundle branch block by combining Lewis' theoretical dextro- and levocardiograms at varying intervals; second, to produce complexes varying between normal and complete bundle branch block by making the usual incision into the right upper portion of the septum, and eliciting right extrasystoles by electrical shock at varying intervals; third, to produce the same variation in complexes by compressing the right septum and permitting the septal myocardium to recover. From these observations, Wilson and Herrmann concluded that the complexes which fulfill Carter's criteria represent complete bundle branch block, and that the atypical complexes with prolonged QRS intervals are due to incomplete bundle branch block.

Stenstroem,[20] in a series of communications (1922, 1924, and 1927), supported Wilson and Herrmann's explanation of atypical bundle branch block, and presented evidence showing that electrocardiograms of transient bundle branch block and of varying forms of bundle branch block were the result of incomplete bundle branch block.

While the cited observations were being made, other studies had been published which threw doubt on the entire orthodox bundle branch block concept. Boden and Neukirch,[21] working with transfused human and animal hearts, cut away the right ventricle and found that the resulting electrocardiogram had the main initial spike downwardly directed; on removal of the left ventricle, the electrocardiogram traced by the right ventricle had its main deflection upwardly directed. They also rotated the heart on its longitudinal and anteroposterior axes, and discovered that the heart's position profoundly affected the form and direction of the ventricular complex. Some years later, Meek and Wilson[22] fully corroborated Boden and Neukirch's observations con-

cerning the effect of cardiac position on the ventricular curves of the electrocardiogram. In 1920, Fahr[23] published an analysis of the human electrocardiogram from which it may be inferred that he questioned Lewis' conception of the levo- and dextrocardiogram. Fahr concluded that Lewis' statement concerning the rotation of the electrical axis in bundle branch block was also probably erroneous, and that the common type of bundle branch block was left, and the less common, right. In spite of these startling reports, the older concepts prevailed. Willius[24] (1929), in his *Clinical Electrocardiograms,* classified bundle branch block complexes as follows:

I. Complete bundle branch block—the complexes which fulfill Carter's criteria.
   a. Right bundle branch block—the common type.
   b. Left bundle branch block—the less common type.

II. Incomplete bundle branch block—the atypical ventricular complexes with a QRS interval of 0.1 second or more.

The same year (1929), a patient with purulent pericarditis entered the University Hospital at Ann Arbor, Michigan. He was operated upon, and the wound, which remained open, exposed the anterior surfaces of the right and left ventricles. The alert workers at the Heart Station of the hospital seized the opportunity to make electrocardiographic studies of the exposed heart. In a series of well-planned and well-executed experiments, they ascertained, first, the spread of the wave of excitation over the anterior surface of the heart; and, second, the form of the extrasystoles originating at the various points on the surface of the two ventricles. They used the technique of Lewis and Rothschild, and employed points analogous to theirs, from which they ascertained the time of arrival of the wave. The readings obtained by Lewis and Rothschild from points on the ventricular surface of the dog heart are consistent with Lewis' theory of the spread of excitation in the ventricles, in that they show that the earliest point of arrival of the wave is on the anterior surface of the right ventricle just over the papillary muscle, and that it arrives later over the conus arteriosus and at points near the atrioventricular groove in the right and left ventricles.

The readings obtained by Barker, Macleod, and Alexander from points *g, b, a,* and *i* (Fig. 4) show that the earliest point of arrival of the wave of excitation is near the atrioventricular groove on the right ventricle and over the conus arteriosus, and that it arrives at an appreciably later time at the "earliest" point of Lewis.

The Michigan investigators also found that concordant as well as discordant extrasystoles could be produced by stimulating both the right and left ventricles, and that, in Lead I, all of the chief initial deflections from the right ventricle are upward, and all from the left ventricle, downward; in Lead III the ectopic beats produced by stimulating the conus and the area adjacent to it in the left ventricle are up-

wardly directed, whereas those from the other exposed regions of the heart point downward.

The factual observations made by Barker, Macleod, and Alexander[9] were soon verified by other investigators, including Marvin and Oughterson[25] and Lundy and Bacon.[26] Kountz, Prinzmetal, Pearson, Koenig, and Smith[27, 28] repeated the experiments of Barker, Macleod, and Alexander on transfused human hearts and on monkey hearts. Their observations, too, support those of the Michigan workers. The St. Louis investigators, making the usual transverse cut into the upper part of the septum of four transfused human hearts, found that, when the cut was made on the left side, the complexes of the common form of bundle branch block were traced, and, when made on the right side, bundle branch block of the less common type developed.

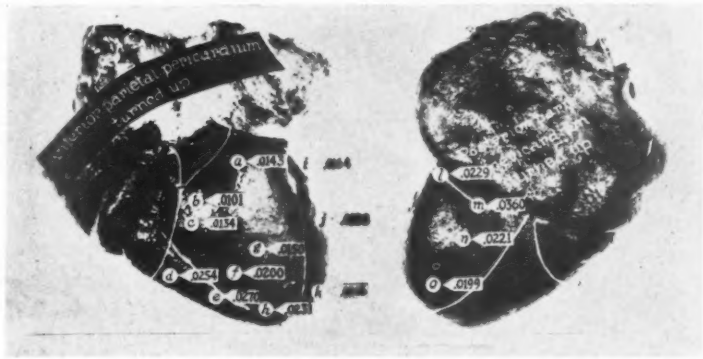


Fig. 4.—Time of arrival of wave of excitation in the human heart. (Barker, Macleod, and Alexander.)

Furthermore, Wilson, Macleod, and Barker,[29] in 1931, carefully reexamined the observations upon which Lewis had based his statement concerning the levo- and dextrocardiogram and the rotation of the electrical axis in bundle branch block, and arrived at the conclucion that the basic data from which Lewis had made his determinations were probably erroneous. By using the second part of the initial ventricular complex instead of the first, as Lewis had done, they showed that the electrical axis swung from right to left in the common form of bundle branch block, so that the movement of the electrical axis was also consistent with the new theoretical site of the lesion in bundle branch block. Fenichel,[30] a year later, published an elaborate and involved analysis of the electrocardiogram, and concluded that the electrical axis rotated in a manner consistent with the European view of bundle branch block. Then, Robb, Easby, and Hiss,[11] in a critical analysis of the methods employed in the determination of the electrical axis, stated that the basic assumptions employed in its determination were not sound.

The meagerness of our own knowledge of the electrophysics of the heart precludes any attempt to evaluate these conflicting observations

and conclusions. Perhaps when cognizance is taken of the form of the distinct muscle bands of which the myocardium is composed, studies like the ones just cited will be more profitable to physiology and medicine.

During this period, evidence had been accumulating from other sorts of experimentation which supported the American view that bundle branch block complexes of the common form were due to disturbances in the left rather than in the right ventricle.

Eppinger and Rothberger had noted in their early experiments concerning bundle branch block that the injured ventricle "limped after" the uninjured; and had been able to demonstrate a slight but detectable delay in the pulse wave coming from the injured ventricle. Other investigators of experimental bundle branch block had verified their observations. Wolferth and Margolies[31] and Braun-Menéndez and Solari[32] were able to demonstrate that in human cases there was a similar lag. Finally, by employing their serial precordial leads, Wilson, Macleod, and Barker[33] were able to show that the wave of excitation appeared late over the left ventricle in the common form of bundle branch block and late over the contralateral ventricle in the rarer form.

Thus, rather clear-cut evidence from various kinds of experimental approach strongly supports the view first expressed by Fahr that the common form of bundle branch block is due to a lesion on the left side of the septum. In spite of this evidence, Katz and Ackerman[34] asserted that it is not safe to make a diagnosis of right- or left-sided bundle branch block from the form of the ventricular complex. They suggested the terms "common" and "less common" instead of left and right bundle branch block, basing their contention on the work of Boden and Neukirch, and of Meek and Wilson, which has already been reviewed, and on their own experiments on the dog, in which they were able to change one type of bundle branch block into the other by extreme rotation of the heart.

Nathanson,[35] Lundy, Treiger, and Davison,[36] and Kountz, Prinzmetal, and Smith[28] also showed that the heart's position in the thorax influenced not only the amplitude, but also the direction of the ventricular complex. Nichol,[37] who repeated the work of Katz and Ackerman, corroborated their findings, but observed that the extreme rotation required for the change from one type of bundle branch block to the other was possible only under experimental conditions. He, therefore, concluded that in human cases of bundle branch block it was safe to designate bundle branch block complexes as either right or left.

The new factual information concerning bundle branch block, secured mostly by American investigators in the last two decades, rendered the older classification of bundle branch block complexes inadequate and obsolete. Further attempts were made, therefore, to classify bundle branch block complexes into more useful and more logical groups. Graybiel and Sprague[38] (1933) found 395 cases of defective

ventricular conduction among 16,000 electrocardiograms. These they arranged into four main groups:

Group I. Left bundle branch block—common type (125 cases).
a. Homophasic type—in which the initial and final ventricular deflection have the same direction (99 cases).
b. Heterophasic type—in which the final deflection is directed oppositely to the main spike.

Group II. Right bundle branch block—less common type (29 cases). Heterophasic only.

Group III. Intermediary type (81 cases).
QRS, slurred; QRS interval more than 0.1 second; T often, but not always, opposite to the main initial deflection. QRS is often similarly directed in Leads I and III. The authors think these represent incomplete block.

Group IV. Slight intraventricular block (160 cases).
QRS, slurred and notched; QRS interval, normal or slightly prolonged; T, variable. The authors consider this group to represent a transitional or slight block.

Graybiel and Sprague found the prognosis similar in all four groups; the average duration of life was one year and two months after discovery of the abnormal tracings. They concluded that the prognosis was not dependent upon the type of ventricular complex, but upon the general condition of the patient.

By employing serial precordial leads, Wilson, Macleod, and Barker[33] discovered that, in all cases of prolonged QRS interval in which a wide S was present in Lead I, regardless of the depth of the S wave and of the amplitude and direction of the ventricular complexes in the other leads, the wave of excitation appeared late over the right side of the heart. They concluded that bundle branch block complexes with a wide S_1 represent right bundle branch block.

Bayley[39] (1934) critically examined all the available cases in the University Hospital at Ann Arbor, Michigan, in which the QRS interval was 0.12 second or more, and the amplitude at least 0.5 cm. in one lead. He thought such cases represented complete bundle branch block. Of the 173 cases examined, 103 were found to be complete left bundle branch block, and 70, right bundle branch block. Bayley divided the cases of right bundle branch block into four groups:

Group I. With characteristic curves of the less common type of bundle branch block (14 cases).

Group II. Differing from Group I in that the amplitude of the R was greater than that of the S (23 cases).

Group III. With a slender, deep spike in Lead III (28 cases).

Group IV. With R absent in Lead III (5 cases).

Bayley found that no single etiologic factor or any particular kind of heart disease was responsible in any of the four groups.

In 1939, Freund and Sokolov[40] reported an analysis of 210 cases of bundle branch block which they classified into four main groups:

Group I. Common type—left bundle branch block.
- a. Homophasic—Graybiel and Sprague (10 cases).
- b. Heterophasic—Graybiel and Sprague (80 cases).

Group II. Less common type—complete right bundle branch block.
- a. Bayley's Group I (14 cases).
- b. Bayley's Group II (18 cases).
- c. Bayley's Group III (21 cases).
- d. Bayley's Group IV (6 cases).
- e. Wilson, Johnston, and Barker's[41] "rare" type (3 cases).

Group III. Bundle branch block without localization characteristics but with a QRS interval of 0.12 second or more (7 cases).

Group IV. Arborization block—with a QRS interval of 0.1 second or more, notching of R, low voltage in all three leads, and absence of the typical diphasic curve; also, cases with a QRS interval of more than 0.12 second, without distinguishing features (50 cases).

Freund and Sokolov found that left bundle branch block of the homophasic type had the best life expectancy (4.7 years). They also found that Group II (a and b) had the average life expectancy for the entire series, but that the survival period for Group II (c) was almost twice as long as that for any other type of right bundle branch block. In the three cases of the "rare type" of right bundle branch block, the condition of the patient was terminal when the electrocardiogram was taken. The prognosis was the worst for the cases that they called arborization block (0.45 of a year).

Finally, Willius,[42] who has been interested in the clinical phases of bundle branch block for decades, with his collaborators, Reeser and Dry, simplified former classifications and recorded life expectancy according to their grouping.

The Rochester investigators questioned the use of the terms "complete" and "incomplete" as applied to bundle branch block, and, on the basis of Yater's[43] histopathologic study, concluded that the lesions in the common type of block occur on the left side, and those in the less common, on the right side. They arranged their cases into:

I. Concordant—the classic form, with the T directed oppositely to the main initial spike.

II. Discordant—the less classic form, with a QRS interval 0.1 second or more, variable amplitude, and the T directed similarly to the main initial deflection in Leads I and III.

III. Bundle branch block of the wide S-wave pattern.

Of the 1,611 cases studied, 756 were concordant, of which 23 were right bundle branch block, and 733, left; 363 cases were discordant;

492 were of the wide S-wave type. The life expectancy of the thee types is graphically shown in Willius' illustration.

The classifications just listed do not appear to dispel the mist which surrounds the bundle branch block concept. Perhaps there is no logical basis for classifying cardiac disorders according to such electrocardiographic patterns. However, there seems to be agreement among the various classifiers that the empiric criteria of Carter are no longer adequate. Most of his imposing list of essential characteristics have been dropped. The only criterion that remains is a prolonged QRS complex, but, even here, there is no agreement in regard to its length. Wilson's assertion that complete bundle branch block is present when the QRS interval is 0.12 second or more is generally accepted, and the consensus among American investigators is that the common type of bundle branch block complex represents left ventricular lag, and the less common, right. But European investigators do not consider the evidence brought forth in America as decisive. In fact, Rothberger and Goebel[44] state that the evidence presented by Barker, Macleod, and Alexander does not support their conclusion. And, since the whole bundle branch block concept has an anatomic basis, Rothberger rightly holds that the location and extent of the blocking lesion, and that alone, should determine whether the block is right or left, complete or incomplete. Since the orthodox conception of cardiac conduction, as well as the bundle branch block concept, is based upon anatomic assumptions, it follows that the whole bundle branch block concept is dependent upon the existence of a specific anatomic structure, the His-Tawara system, and upon the presence of demonstrable morbid changes in one or the other branch of the His bundle.

Let us, therefore, next consider the evidence for these assumptions. The orthodox concept of cardiac conduction assumes that the myogenic atrioventricular bundle begins in dendrite-like muscle fasciculi lying among atrial muscle fibers. These gather the wave of excitation from the atrial muscle, and shunt it into a compact muscular bundle where the cardiac impulse is held insulated from the rest of the myocardium as it travels from behind the central fibrous body to the level of the septal papillary muscles. Here it bursts with explosive suddenness over the entire subendocardial ventricular musculature, whence it travels radially through the myocardium. The orthodox theory is based on the assumption that the myocardium is a syncytium. We wonder how anyone can look at the myocardium either microscopically or grossly and still retain this conception. To be sure, the branches of individual myocardial muscle cells intermingle with one another, but, from the very time in embryonic life that the muscle fibers are differentiated, the individual cell borders are distinct, and the fasciculi of muscle fibers within the myocardium are surrounded by connective tissue sheaths as distinct as those found in skeletal muscle (Fig. 5). Recently, the gross anatomy of the muscle bands which compose the myocardium of the ventricle has been meticulously described and profusely illustrated in the articles

published by Robb.[45] The separate vascular supply, as well as the origin and insertion of the muscles revealed in the specimens prepared by Robb, needs but to be seen to be appreciated. These muscle bands have been seen for many centuries by the anatomists who have looked for them. They may be seen by anyone who will take the time to remove the visceral pericardium and do a careful dissection. As is clearly shown by the dissections of Robb (Fig. 6), the muscles of the ventricular myocardium have their origin and insertion in the fibrous ring which separates the atria from the ventricles. All the muscles with the exception of the deep bulbospiral are common to both ventricles, so that both ventricles function as one, a fact brought out by Harvey more than three hundred years ago. We[2] have already

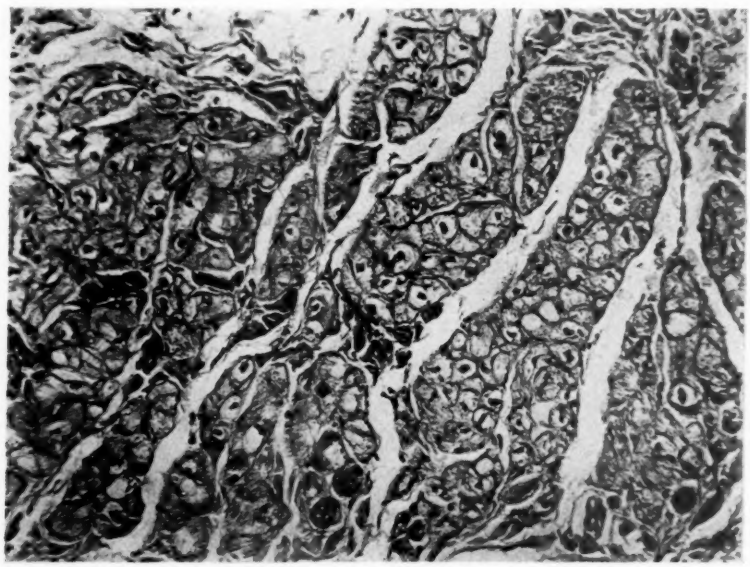


Fig. 5.—Heart muscle fasciculi showing interstitial connective tissue.

shown that large numbers of ganglion cells are located in the atrioventricular groove near the origin of these muscles. Therefore, until it is demonstrated that these muscles are not activated by the nerve elements present at their origin, until it is shown that the wave of excitation does not travel along the muscle bands in the heart muscles as it does in the skeletal muscles, and until it is disproved that the contraction and relaxation of the muscles of the ventricles do not proceed in the same efficient and purposeful manner as is the case in the limb muscles, it seems illogical and unnecessary to assume that the activation of the ventricle should be wholly dependent upon a microscopic muscle fasciculus.

It seems appropriate to sketch briefly the evolution of the anatomic basis of the modern concept of cardiac conduction. When, in 1883, Gaskell[46] noted that the tortoise ventricle continued to beat normally

after zigzag cuts in the adjoining auricular wall, he felt certain that he had destroyed all nerve pathways to the lower chamber, and rejuvenated the myogenic conception of impulse transmission to explain the synchronous contraction of the heart chambers. Around the opening of the atrioventricular valves, he found muscle fibers which were paler and more slender than the rest of the muscle elements, assumed that the paler ones were more embryonic than their fellows, and concluded that impulse conduction was their special function.

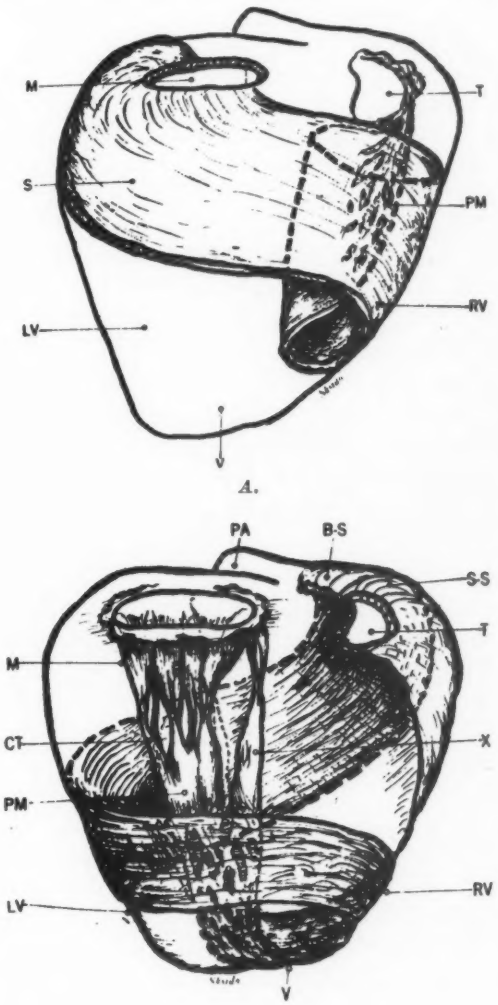


Fig. 6.—*A* and *B*. Cardiac muscle bands. (Robb.)

In 1893, Kent[47] reported that he had found in man and other mammals *numerous* muscle bridges between the atria and the ventricles in the atrioventricular groove; in the same year, His, Jr.,[48] stated that, after diligent search, he had discovered in man and other mammals *a* muscle

bundle originating in the atrial septum and extending into the left ventricle. But the illustrations of the bundle which accompany His' communication bear little resemblance to subsequent pictures of the His bundle.

In 1906, Tawara,[49] a Japanese pupil of Aschoff, published his famous monograph on the cardiac conducting system in mammals. Tawara accurately described a part of the Purkinje system in ungulates, and noted that the main trunk and the branches of what we have called the Purkinje bundle were isolated from the rest of the myocardium by a connective tissue covering. Tawara saw *with the naked eye* a similar bundle in man and dog.

In 1906, Keith and Flack[50] reported that they had examined 130 human hearts and stated: "In properly prepared hearts the bundle is *big* enough to be found and dissected out by knife and forceps alone."

In 1913, Tandler,[51] another pupil of Aschoff, described and clearly pictured the His bundle in man. Since that time the His bundle has been seen and its gross appearance described by Moenckeberg,[52] Spalteholz,[53] Yater, et al.,[54] and others.

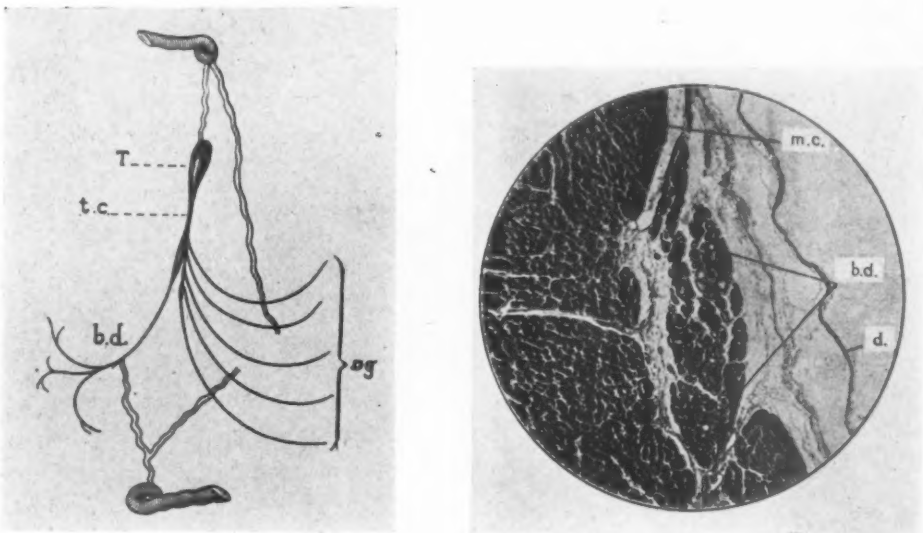
Similarly, the conducting system of the dog has been described as almost identical with that of man. Before 1925, all experimental investigators of bundle branch block *saw* the branches of the His bundle through the semitransparent endocardium in the dog. Lewis and Rothschild[8] present remarkable drawings of the right and left branches of the His bundle and of the entire Purkinje system in the dog. In the latest edition of his book, Lewis[55] states that the branches of the His bundle *can be seen* through the endocardium of the dog, although he admits that the branches are not distinct. Rothberger and Winterberg's[5] "drawings from nature" show not only the main branches, but also the twigs of the right and left branches in the dog.

In 1931, Mahaim[56] published his monograph on the His-Tawara system. In it occurs the astonishing statement that the His bundle in man is *not* visible to the naked eye, that it can be found and followed only by means of serial sections, and that *every* section of the series must be saved lest a branch or a lesion be lost (Fig. 7).

Thus, it appears that, like a new star, the His bundle could be readily seen for nearly three decades, after which it suddenly shrank to a magnitude not visible to the naked eye! For, from the time of Mahaim's monograph until now, we have not encountered in the literature any claim by experimental or clinical students of the conducting system that they have seen the His bundle or its branches, either in dog or in man, with the naked eye.

Students of the anatomy of the system now stress that it must be located and studied by means of serial sections. Not all of them urge that each section of the series be studied, but they emphasize that great care and almost superhuman skill is required to study the normal His bundle and its histopathology. The descriptions of the histologic structure of the His-Tawara system as given by Tawara, Moenckeberg, Lewis,

Yater, and Mahaim can equally well be labeled descriptions of ordinary myocardial fibers; and the excellent drawing of the histologic structure of the left branch of the His bundle in Cohn and Trendelenburg's[57] article, and the remarkably clear microphotographs of the bundle branches in Mahaim's monograph (Fig. 7) are indistinguishable from those of the neighboring muscle fasciculi. None of the students of the particular muscle fasciculus which is called the His bundle mentions the obvious fact that there are literally hundreds of muscle fasciculi in the ventricular subendocardium which can be followed with relative ease by means of serial sections. Such muscle fasciculi can also be separated from their fellows by careful dissection.



A. *B.*

Fig. 7.—The His-Tawara system. (Mahaim.) *A*, Schematic drawing. *B*, Microscopic structure—right branch.

In the particular muscle fasciculi which have been thought to be the branches of the His bundle are to be found the blocking lesions which are assumed to be the direct cause of the bundle branch block complexes. We, therefore, logically pass to a review of the studies of the histopathology of the branches of the His bundle.

In order to avoid confusion, the discussion will be limited to the histologic observations in the *common* form of bundle branch block. Those in the case of the less common form are similar. It should be noted that the observations listed have been obtained from a study of serial sections, and that the individual worker who obtained the information stressed the fact that the studies had been done with unusual care. The relation of the blocking lesions which were found in cases of the common form of bundle branch block to the complexes traced by the living heart has been epitomized in Table I. It is clear that, in approximately one-fourth of the cases, no blocking lesions were found,

that in a little more than one-third of the cases the blocking lesions were found on the left side, and that in the remainder they were on the right side.

TABLE I

HISTOLOGIC OBSERVATIONS IN THE COMMON TYPE OF BUNDLE BRANCH BLOCK

AUTHORS	NUMBER OF CASES	RIGHT SIDE OF SEPTUM	LEFT SIDE OF SEPTUM
Eppinger and Stoerck	2	Blocking Lesions	None
Cohn and Lewis	4	No Blocking Lesion	No Blocking Lesion
Oppenheimer and Pardee	1	None	Blocking Lesion
Oppenheimer and Oppenheimer	3	None	Blocking Lesion
Oppenheimer and Oppenheimer	1	Slight Fibrosis	Blocking Lesion
Taussig	1	Blocking Lesion	None
Mahaim	7	Blocking Lesions	Fibrosis
Yater	3	Fibrosis	Blocking Lesions
Yater	1	No Blocking Lesion	No Blocking Lesion
Summation	23	10 Blocking Lesions 5 No Blocking Lesion	8 Blocking Lesions 5 No Blocking Lesion

CONCLUSIONS

From the reviewed observations the following conclusions appear justifiable:

1. The common type of bundle branch block complex represents left ventricular lag; the less common type represents lag of the right ventricle. The many attempts which have been made to group the complexes into logical classes are of scant practical value in the diagnosis and prognosis of cardiac disease.
2. The evidence presented to prove the existence of a special conducting system is irrelevant and immaterial.
3. The microscopic areas of fibrosis which have been found in the upper part of the interventricular septum in cases of bundle branch block bear no causal relation to the grossly abnormal ventricular deflections that have a prolonged QRS interval because:
   a. Such lesions are absent in a considerable number of cases of bundle branch block.
   b. When small fibrous lesions are found in either right or left bundle branch block, they occur with about equal frequency on both sides of the septum.
4. It is, therefore, apparent that further search should be made for the cause of the grossly abnormal complexes which are now thought to indicate bundle branch block.

"NACHHINKEN"

In their earliest experiment on bundle branch block, Eppinger and Rothberger observed that, while the wide diphasic ventricular complexes were being traced, the injured ventricle was dilated and "limped after"

the contralateral ventricle. This "nachhinken" has been noted by practically all experimental observers of bundle branch block. More recently, such delayed activation of the ventricle has been demonstrated by Wilson, Macleod, and Barker,[33] Wolferth and Margolies,[31] and Braun-Menéndez and Solari[32] in cases of human bundle branch block. It is, therefore, apparent that the so-called bundle branch block complexes may be the electrocardiographic manifestation of a "failing" right or left ventricle; if so, any factor or factors which can produce this unilateral lag may be responsible for bundle branch complexes.

Many excellent studies of human bundle branch block have been reported: Carter,[15] Oppenheimer and Rothschild,[14] Willius,[58] Herrick and Smith,[59] and Hill.[60] There is striking uniformity in the clinical observations made by these investigators. It is apparent that human bundle branch block complexes are traced by sick hearts. (The bundle branch block complexes with a short P–R interval are not included in this discussion because the nature of these is different from that of the others.) The factors which have crippled the hearts in cases of bundle branch block are identical with those which lead to cardiac failure, with or without these abnormal electrocardiograms. Thus, when bundle branch block complexes are obtained in the young, they are found in connection with congenital defects, hyperthyroidism, or infections of the heart; after the age of 40 years, they are associated, as a rule, with hypertension, coronary atherosclerosis, or a combination of these conditions. Therefore, it occurred to us that the same factors might bring about bundle branch block complexes whenever they produce failure in one ventricle while the other is relatively normal. Out of these considerations grew the following working hypothesis:

Bundle branch block complexes are caused by:

a. abnormal unilateral strain.

b. unilateral ventricular coronary insufficiency.

c. a combination of (a) and (b).

In our next communication we shall present the evidence that we have obtained pertinent to this hypothesis.

REFERENCES

1. Eppinger, H., and Rothberger, C. J.: Zur Analyze des Elektrokardiogramms, Wien. klin. Wchnschr. **22**: 1091, 1909.
2. Glomset, D. J., and Glomset, A. T. A.: A Morphologic Study of the Cardiac Conduction System in Ungulates, Dog, and Man. Part II: The Purkinje System, AM. HEART J. **20**: 677, 1940.
3. Eppinger, H., and Rothberger, C. J.: Ueber die Folgen der Durchschneidung der Tawaraschen Schenkel des Reizleitungssystems, Ztschr. f. klin. Med. **70**: 1, 1910.
4. Barker, L. F., and Hirschfelder, A. D.: The Effects of Cutting the Branch of the His Bundle Going to the Left Ventricle, Arch. Int. Med. **4**: 193, 1909.
5. Rothberger, C. J. and Winterberg, H.: Experimentelle Beitraege zur Kenntnis der Reizleitungs-stoerungen in den Kammern des Saeugetierherzens, Ztschr. f. d. ges. exper. Med. **5**: 264, 1917.
6. Eppinger, H., and Stoerck, O.: Zur Klinik des Elektrokardiogramms, Ztschr. f. klin. Med. **71**: 157, 1910.

7. Lewis, T.: The Spread of the Excitatory Process in the Vertebrate Heart. Part III. The Dog's Ventricle, Phil. Trans. Roy. Soc. Lond. B. **207**: 247, 1916.
8. Lewis, T., and Rothschild, M. A.: The Excitatory Process in the Dog's Heart. Part II. The Ventricles, Phil. Trans. Roy. Soc. Lond. B. **206**: 181, 1915.
9. Barker, P. S., MacLeod, A. G., and Alexander, J.: The Excitatory Process Observed in the Exposed Human Heart, AM. HEART J. **5**: 720, 1930.
10. Robb, J. S., and Robb, R. C.: The Excitatory Process in the Mammalian Ventricle, Am. J. Physiol. **115**: 43, 1936.
11. Robb, J. S., Easby, M., and Hiss, J. G. F.: Experimental Interference With Conduction in the Heart, Am. J. M. Sc. **188**: 835, 1934.
12. Carter, E. P.: Clinical Observations on Defective Conduction in the Branches of the Auriculo-Ventricular Bundle, Arch. Int. Med. **13**: 803, 1914.
13. Cohn, A. E., and Lewis, T.: The Pathology of Bundle Branch Lesions of the Heart, Proc. New York Path. Soc. **14**: 207, 1914.
14. Oppenheimer, B. S., and Rothschild, M. A.: Electrocardiographic Changes Associated With Myocardial Involvement, J. A. M. A. **69**: 429, 1917.
15. Carter, E. P.: Further Observations on the Aberrant Electrocardiogram Associated With Sclerosis of the Atrioventricular Bundle Branches and Their Terminal Arborizations, Arch. Int. Med. **22**: 331, 1918.
16. Willius, F. A.: Arborization Block, Arch. Int. Med. **23**: 431, 1919.
17. Smith, F. M.: Experimental Observations on the Atypical QRS Waves of the Electrocardiogram of the Dog, Arch. Int. Med. **26**: 205, 1920.
18. Wilson, F. N., and Herrmann, G. R.: Bundle Branch Block and Arborization Block, Arch. Int. Med. **26**: 153, 1920.
19. Wilson, F. N., and Herrmann, G. R.: An Experimental Study of Incomplete Bundle Branch Block and of the Refractory Period of the Heart of the Dog, Heart **8**: 229, 1921.
20. a. Stenstroem, N.: Contributions to the Knowledge of Incomplete Bundle Branch Block in Man, Acta med. Scandinav. **57**: 385, 1922.
    b. Stenstroem, N.: An Experimental and Clinical Study of Incomplete Bundle Branch Block, Acta med. Scandinav. **60**: 552, 1924.
    c. Stenstroem, N.: Further Experience on Incomplete Bundle Branch Block in Man, Acta med. Scandinav. **67**: 353, 1927.
21. Boden, E., and Neukirch, P.: Elektrokardiographische Studien am isolierten Saeugetier-und Menschenherzen bei direkter und indirekter Ableitung, Arch. f. d. ges. Physiol. **171**: 146, 1918.
22. Meek, W. J., and Wilson, A.: The Effect of Changes in Position of the Heart on the QRS Complex of the Electrocardiogram, Arch. Int. Med. **36**: 614, 1925.
23. Fahr, G.: An Analysis of the Spread of the Excitation Wave in the Human Ventricle, Arch. Int. Med. **25**: 146, 1920.
24. Willius, F.: Clinical Electrocardiograms: Their Interpretation and Significance, Philadelphia and London, 1929, W. B. Saunders Company.
25. Marvin, H. M., and Oughterson, A. W.: The Form of Premature Beats Resulting From Direct Stimulation of the Human Ventricles, AM. HEART J. **7**: 471, 1932.
26. Lundy, C. J., and Bacon, C. M.: Premature Left Ventricular Beats From Electrical Stimulation of Exposed Human Heart, Arch. Int. Med. **52**: 30, 1933.
27. Kountz, W. B., Prinzmetal, M., Pearson, E. F., and Koenig, K. F.: The Effect of Position of the Heart on the Electrocardiogram, AM. HEART J. **10**: 605, 1935.
28. Kountz, W. B., Prinzmetal, M., and Smith, J. R.: The Effect of Position of the Heart on the Electrocardiogram, Observations Upon the Electrocardiogram in the Monkey, AM. HEART J. **10**: 623, 1935.
29. Wilson, F. N., Macleod, A. G., and Barker, P. S.: The Interpretation of Initial Deflections of the Ventricular Complex of the Electrocardiogram, AM. HEART J. **6**: 637, 1931.
30. Fenichel, N. M.: An Analysis of the QRS Complex of the Electrocardiogram, AM. HEART J. **7**: 514, 1932.
31. Wolferth, C. C., and Margolies, A.: Asynchronism in Contraction of the Ventricles in the So-Called Common Type of Bundle Branch Block: Its Bearing on the Determination of the Side of the Significant Lesion and on the Mechanism of Split First and Second Heart Sounds, AM. HEART J. **10**: 425, 1935.

32. Braun-Menéndez, E., and Solari, L. A.: Ventricular Asynchronism in Bundle Branch Block, Arch. Int. Med. **63**: 830, 1939.
33. Wilson, F. N., Macleod, A. G., and Barker, P. S.: The Order of Ventricular Excitation in Human Bundle Branch Block, AM. HEART J. **7**: 305, 1932.
34. Katz, L. N., and Ackerman, W.: The Effect of the Heart's Position on the Electrocardiographic Appearance of Ventricular Extra-systoles. J. Clin. Investigation **11**: 1221, 1932.
35. Nathanson, M. H.: Electrocardiographic Study of Movements of the Heart With Change of Posture, Proc. Soc. Exper. Biol. & Med. **28**: 766, 1931.
36. Lundy, C. J., Treiger, I., and Davison, R.: Ventricular Extrasystoles Induced by Electrical Stimulation of the Exposed Human Heart Rotated Thirty Degrees Counterclockwise on Its Vertical Axis, AM. HEART J. **17**: 85, 1939.
37. Nichol, A. D.: The Interpretation of Lead Inversion in Bundle Branch Block, AM. HEART J. **9**: 72, 1933.
38. Graybiel, A., and Sprague, H. B.: Bundle Branch Block; Analysis of 395 Cases, Am. J. M. Sc. **185**: 395, 1933.
39. Bayley, R. H.: The Frequency and Significance of Right Bundle Branch Block, Am. J. M. Sc. **188**: 236, 1934.
40. Freund, H. A., and Sokolov, R.: Bundle Branch Block; Criteria of Classification, Diagnosis and Prognosis; A Study of 210 Cases, With Follow-up Data, Arch. Int. Med. **63**: 318, 1939.
41. Wilson, F. N., Johnston, F. D., and Barker, P. S., Electrocardiograms of an Unusual Type in Right Bundle Branch Block, AM. HEART J. **9**: 472, 1934.
42. Reeser, R., Willius, F. A., and Dry, T. J.: Life Expectancy in Conductive Disturbances Affecting the Ventricular Complexes of the Electrocardiogram. II. Special Consideration of Bundle Branch Block With Concordant Graphs and With Discordant Graphs. Arch. Int. Med. 67: 1027, 1941.
43. Yater, W. M.: Pathogenesis of Bundle Branch Block, Arch. Int. Med. **62**: 1, 1938.
44. Rothberger, C. J., and Goebel, F.: Zur Diagnose des Schenkelblocks, Ztschr. f. klin. Med. **123**: 460, 1933.
45. Robb, J. S.: The Rôle of Muscle Bundles in Ventricular Conduction, M. & S. Year-Book, Physicians Hosp., Plattsburgh **1**: 210, 1929.
46. Gaskell, W. H.: On the Innervation of the Heart With Especial Reference to the Heart of the Tortoise, J. Physiol. **4**: 43, 1883.
47. Kent, A. F. S.: Researches on the Structure and Function of the Mammalian Heart, J. Physiol. **14**: 233, 1893.
48. His, W., Jr.: Die Thaetigkeit des embryonalen Herzens und deren Bedeutung fuer die Lehre von der Herzbewegung beim Erwachsenen, Arb. a. d. med. klin. zu Leipz. 14, 1893.
49. Tawara, S.: Das Reitzleitungssystem des Saeugetierherzens, Jena, 1906, Gustav Fischer.
50. Keith, A., and Flack, M.: The Auriculo-Ventricular Bundle of the Human Heart, Lancet **2**: 359, 1906.
51. Tandler, J.: Anatomie des Herzens, Jena, 1913, Gustav Fischer.
52. Moenckeberg, J. G.: Untersuchungen ueber das Atrioventrikulaerbuendel im menschlichen Herzen, Jena. 1908, Gustav Fischer.
53. Spalteholz, W.: Hand Atlas of Human Anatomy, Philadelphia, 1937, J. B. Lippincott Company, vol. II.
54. Yater, W. M., Osterberg, A. E., and Hefke, H. W.: Chemical Determination of the Glycogen Ratio in the Bundle of His and the Cardiac Muscle in Man and in the Horse, Arch. Int. Med. **45**: 760, 1930.
55. Lewis, T.: The Mechanism and Graphic Registration of the Heart Beat, ed. 3, London, 1925, Shaw & Sons Ltd.
56. Mahaim, I: Les Maladies Organiques du Faisceau de His-Tawara, Paris, 1931, Masson & Cie.
57. Cohn, A. E., and Trendelenburg, W.: Untersuchungen zur Physiologie des Uebergangbuendels am Saeugetierherzen, nebst mikroskopischen Nachpruefungen, Arch. f. d. ges. Physiol. **131**: 1, 1910.
58. Willius, F. A.: Clinical Features of Cases Exhibiting Electrocardiograms Conforming to Those of Experimental Complete Bundle Branch Block, AM. HEART J. **1**: 576, 1926.
59. Herrick, J. B., and Smith, F. M.: Clinical Observations on Block of the Branches of the Auriculoventricular Bundle, Am. J. M. Sc. **164**: 469, 1922.
60. Hill, I. G. W.: Bundle Branch Block; Clinical and Histological Study, Quart. J. Med. **23**: 15, 1930.

STUDIES ON UNIPOLAR LEADS

IV. The Effects of Digitalis

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INTRODUCTION

FOR the past three years we have been conducting studies on the use and application of unipolar leads, particularly augmented, unipolar, extremity leads (aV- leads). In several previous publications, the principles and patterns of these leads have been described,[1, 2] as well as characteristic patterns with myocardial infarction when standard leads are normal.[2, 3]

We felt that this advantage of aV- leads in detecting minimal electrocardiographic changes might be put to further use in the study of other factors affecting the electrocardiogram.

In this paper, our observations on the effects of digitalis on augmented unipolar extremity leads and on unipolar precordial leads are described.

MATERIAL AND METHOD

Although we have on file unipolar records of over 3,000 patients, of whom 500 had been digitalized, for this study we selected and observed 21 cases, both before and after digitalization. Of this group, five had normal hearts, four had rheumatic heart disease, six had hypertensive cardiovascular disease, three had abnormal electrocardiographic patterns without a history of heart disease (cases of severe secondary anemia due to duodenal ulceration), and three were convalescing from recent attacks of myocardial infarction. The acute attack in each of these cases had occurred approximately five weeks previously. None of these patients had ever received digitalis.

Routine digitalization was produced with tablets of powdered *Digitalis purpurea* in the following way: 6 grains were given every eight hours for three doses, then 3 grains a day for four days.

Electrocardiograms were taken a few hours before digitalization and five days later. In all these cases there was a previous electrocardiogram taken before the start of the experiments. Comparison of this with the control electrocardiogram showed, in all cases, no change.

Seven leads were taken. First, the three standard leads. Then, using the author's indifferent electrode of zero potential,[1] aV- leads[1] and a unipolar precordial lead, V_4, with the electrode at the fifth intercostal space in the midclavicular line, were taken.[1, 4] All records were taken with the patients recumbent.

In this study we were not interested in the effects of minimal doses of digitalis on the electrocardiogram.

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From the Department of Medicine, Lincoln Hospital, New York, Dr. Leander H. Shearer, Director.

RESULTS

A. Unipolar Extremity Leads:

1. *P Wave and P-R Interval.*—No characteristic changes in the size and shape of the P wave were noted. The P-R interval was, for the most part, not affected by the amount of digitalis used. Occasionally a lengthening of the P-R interval was noted.

2. *QRS Interval.*—No change in the duration of the QRS interval was noted.

3. *Amplitude of the QRS Complex.*—There was no constant pattern of change in the amplitude of the QRS complex; in one lead the amplitude might be larger, and, in another, smaller than before digitalis administration. However, since the amplitude of QRS in unipolar extremity leads varies directly with the electrical axis of the body,[2] we thought it might be interesting to ascertain whether there was any shift of the electrical axis. We therefore calculated the changes in the electrical axis of the heart directly from the aV- leads.[5]

In this series of cases, the average change in angle α was +5°. In five of our records, no appreciable change was noted. In one case, there was a change of −5°. Changes as high as +15° C. were observed in four records.

4. *The Q-T Interval.*—In ascertaining the effect of digitalis on the Q-T interval, recourse was made to the formula of Fredericia,[6] namely, $Q\text{-}T = 8.22\ \sqrt[3]{R\text{-}R}$,* in which the Q-T interval is described as a function of the ventricular rate.

The Q-T values were calculated as follows: First, the theoretical value was calculated by Fredericia's formula. This was compared to the actual value, read directly from the electrocardiogram. The relation of the actual to the theoretical Q-T value was then expressed as a percentage. This procedure was carried out with the records taken both before and after digitalization. This permits comparison of the two percentages. In Table I, these values are given for the cases illustrated.

Without exception, the Q-T interval was shortened, proportionately, more than could be expected from any change in ventricular rate. In fact, since slowing of the rate was the usual occurrence, lengthening of the Q-T interval would have been expected from the formula.

5. *The RS-T Segment and the T Wave.*—After the administration of digitalis, the RS-T segment and the T wave of the aV- leads always tend to deviate in the direction opposite to that which T originally had, irrespective of the characteristics of the electrocardiogram. Generally, this is also in the direction opposite to that of the main ventricular complex.

The following is a description of these changes in more detail in a typical case (Fig. 1): If T is originally (+), the RS-T segment, begin-

*The Q-T and R-R intervals are expressed in terms of hundredths of a second. Thus, 0.36 second is expressed 36.

TABLE I

THE Q-T INTERVAL BEFORE AND AFTER DIGITALIZATION*

CASE NUMBER		ACTUAL Q-T INTERVAL (SEC.)	VENTRICULAR RATE	R-R INTERVAL (SEC.)	PERCENTAGE OF FORMULA $Q\text{-}T = 8.22\ \sqrt[3]{R\text{-}R}$ (%)
700	before	.32	88	.64	97.3
	after	.28	75	.80	79.1
741	before	.38	68	.88	107.2
	after	.36	60	.88	94.7
702	before	.42	55	1.04	108.6
	after	.36	59	1.01	94.1
706	before	.36	60	1.00	109.1
	after	.32	60	1.00	96.7
721	before	.42	75	.80	119.0
	after	.32	75	.80	90.3
740	before	.36	60	1.00	94.6
	after	.34	65	.92	75.3
749	before	.36	75	.80	101.1
	after	.34	78	.76	97.7

*For details see text.

ning slightly below the isoelectric line, slants obliquely in a (–) direction and fuses with T, which has completely changed its own direction and is now also (–). There is then an abrupt rise to the isoelectric line. If T is (–), the reverse conditions hold.

These changes may or may not be apparent in all three aV- leads. Furthermore, the RS-T slope is often not so oblique, and may have a gentle curve downward (Fig. 4, aVf lead), or a gentle upcurve (Fig. 7, aVf lead). When minimal changes are present, the only evidence may be a decrease in the amplitude of T. This occurs irrespective of whether T had originally been (+) or (–) (Fig. 5, aVf Lead; Fig. 2, aVl lead).

As was just mentioned, these changes were found in the electrocardiograms of both normal and abnormal hearts, except that, in our three cases of recent myocardial infarction, the changes were minimal and consisted for the most part of slight diminution of the T wave. In one case there was a reversal of T.

When the changes in the aV- leads are compared with those in the standard leads, the results are very interesting.

In Case 702 (Fig. 3), the standard leads showed a diminution of the T wave, whereas the aV- leads not only showed this, but, in the aVl lead, there was complete reversal of the direction of T, which became (+) after being deeply (–).

In Case 706 (Fig. 4), again, there was only a slight decrease in the amplitude of T in Leads I and II, whereas, in the aVf lead, T became (–) instead of (+).

In Case 740 (Fig. 6), the patterns of left ventricular preponderance showed but little evidence of any digitalis effect, whereas, in the aVf lead, T changed from (+) to (–).

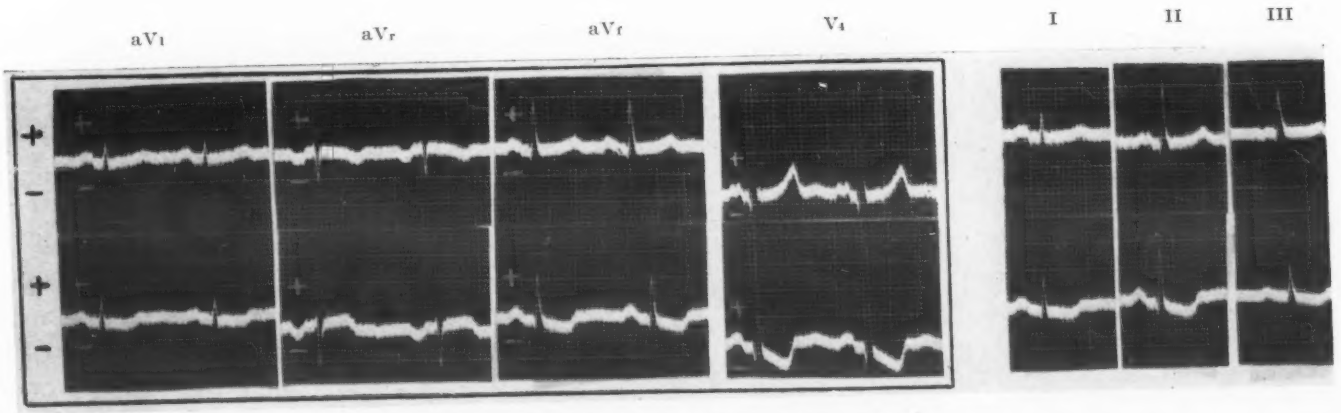

Fig. 1.—Case 700, male, 31 years of age, normal.

Figs. 1 to 7

The effects of digitalis on augmented unipolar extremity leads (aV- leads*) and unipolar precordial leads.
Upper row—before digitalization.
Lower row—after digitalization.

*In all illustrations in this article the aVl lead records potentials from the left arm, the aVr lead records potentials from the right arm, and the aVf lead records potentials from the left leg.

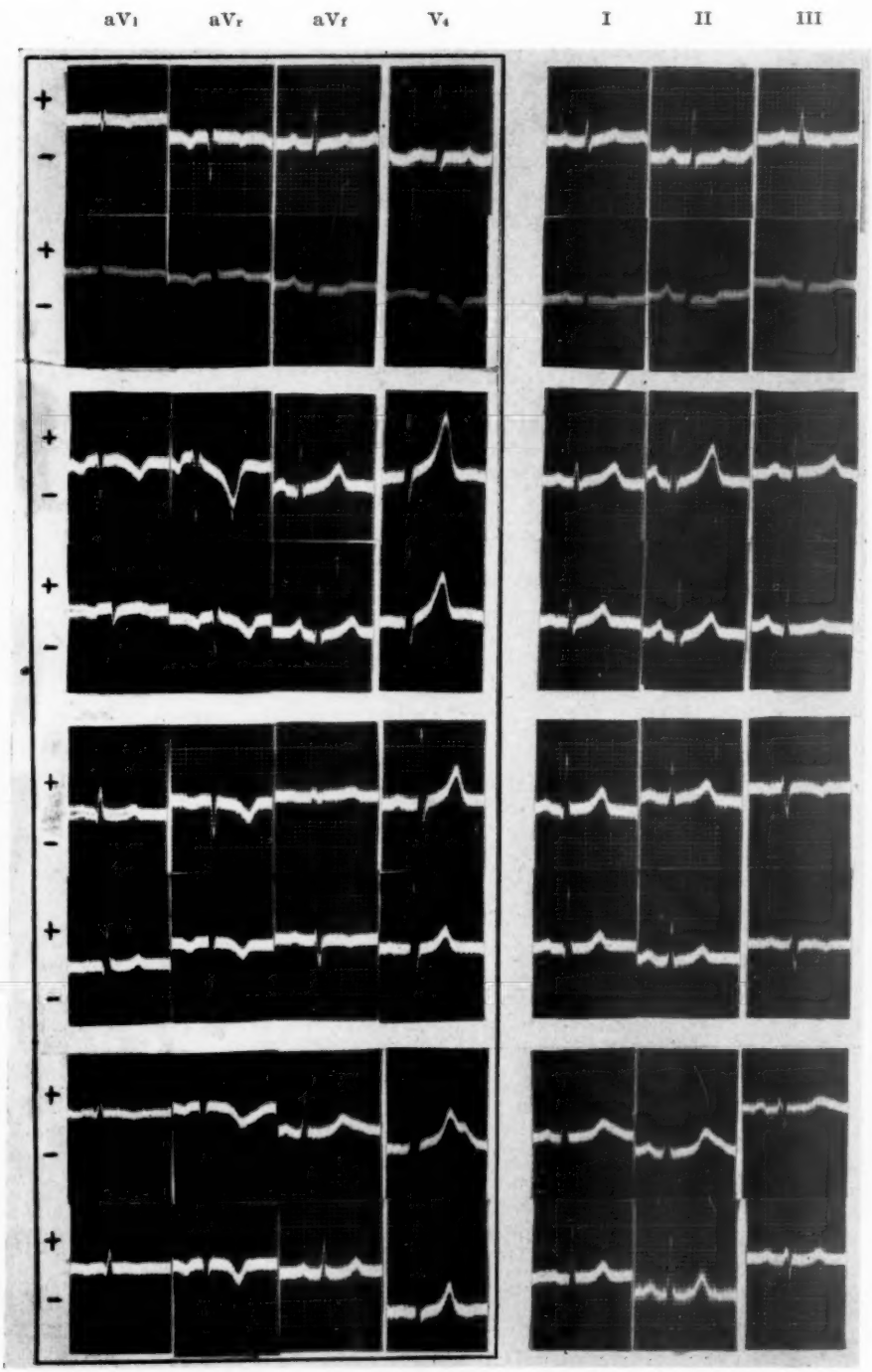

Fig. 2.

Fig. 3.

Fig. 4.

Fig. 5.

Fig. 2.—Case 748, female, 43 years of age, rheumatic heart disease, mitral insufficiency and stenosis.

Fig. 3.—Case 702, male, 33 years of age, bleeding duodenal ulcer, secondary anemia.

Fig. 4.—Case 706, male, 51 years of age, normal.

Fig. 5.—Case 721, male, 50 years of age, bleeding duodenal ulcer, secondary anemia.

Also, in Case 749 (Fig. 7), another example of left ventricular preponderance, the T of the aVf lead showed a very definite change from (–) to (+) polarity, although the standard leads before and after digitalization were quite similar.

B. Unipolar Precordial Leads: The P wave, P-R interval, QRS interval, and Q-T interval were the same as in aV- leads.

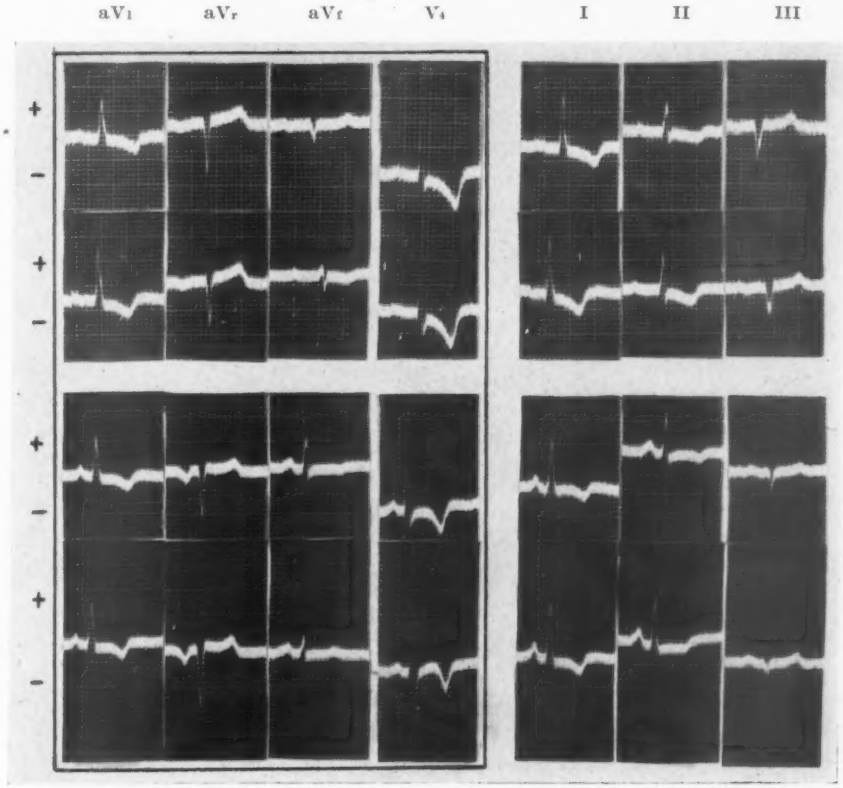

Fig. 6.

Fig. 7.

Fig. 6.—Case 740, female, 47 years of age, hypertension.
Fig. 7.—Case 749, female, 63 years of age, hypertension.

1. *Amplitude of the QRS Complex.*—No characteristic change in the amplitude of QRS in the precordial leads was noted. In many of the records there was a slight decrease.

2. *The RS-T Segment and T Wave.*—In precordial leads, digitalis always causes the RS-T segment and T wave to move in a downward (negative) direction. If the RS-T and T are originally directed downward, as in cases of ventricular preponderance, the only effect is that the angle at which the RS-T segment becomes (–) is made more acute (Figs. 6 and 7). When T is upright, the changes are very similar to those in the aV- leads with an upright T. A slight effect consists merely in a decrease of the amplitude of T (Fig. 3), whereas, with maximal

effect, the RS-T segment, beginning below the isoelectric line, runs obliquely downward, fuses with the (–) T, and sharply rises to the isoelectric line (Fig. 1). The slope of the RS-T may be straight (Fig. 1), or may have a gentle downward curve (Fig. 2).

3. *The U Wave.*—The U wave, usually not conspicuous, was present in the precordial leads in seven of our cases. The effect of digitalis on the U wave was as follows: in three there was no change, in two, there was a slight diminution in the amplitude of U, and, in two cases, U became (–) instead of (+) (Fig. 5).

DISCUSSION

Our results compare favorably, in so far as they can be compared, with those reported in the literature for the standard and ordinary precordial leads. There have been conflicting reports concerning the effect of digitalis on the amplitude of the QRS in standard leads.[7, 8] Our data, showing that there is a change in the electrical axis, probably explain this.

The decrease in the Q-T interval is generally regarded as a manifestation of digitalization,[8] although this, too, has been questioned,[9] and inversion of T and the depression of the RS-T segment were described many years ago.[10, 11]

With respect to the effects of digitalis on precordial leads, although varied changes have been described, such as raising or lowering of the RS-T segment and increased or decreased T waves,[12] our results are similar to those currently accepted.[13]

CONCLUSIONS

We find that the effects of digitalis on the unipolar leads of the electrocardiogram are quite constant, and occur irrespective of the nature of the cardiac condition or of the previous electrocardiographic pattern.

In augmented unipolar extremity leads (aV- leads), both the RS-T segment and the T wave tend to deviate in a direction opposite to that in which T was previously directed. Thus, if T had been (+), the direction of deviation is (–), and vice versa. When this is marked, RS-T moves obliquely downward or upward, as the case may be, fuses with T, and then abruptly runs to the isoelectric line. Along with these changes, there may be an increase in the P-R interval, a decreased Q-T interval, and a slight shift in the electrical axis of the heart, usually in a clockwise direction. Minimal T changes consist in merely a decrease in amplitude.

It was also observed that, in cases in which the standard leads showed only inconstant or no changes, in one or more of the aV- leads a characteristic and definite reversal of direction of T was observed.

In unipolar precordial leads the changes were similar, but the direction of deviation was always in a (–) downward direction. A decrease in the amplitude of U may also be observed, and also a reversal of its polarity.

REFERENCES

1. Goldberger, E.: A Simple Electrocardiographic Indifferent Electrode of Zero Potential, and a Technique of Obtaining Augmented Unipolar Extremity Leads (aV- Leads), AM. HEART J. **23**: 483, 1942.
2. Goldberger, E.: The aVl, aVr, and aVf Leads, AM. HEART J. **24**: 378, 1942.
3. Goldberger, E.: The Use and Advantages of Augmented Unipolar Extremity Leads (aV- Leads) in the Electrocardiographic Diagnosis of Myocardial Infarction (Coronary Thrombosis and Acute Coronary Insufficiency), New York State J. Med. **43**: 961, 1943.
4. Johnston, F. D., Rosenbaum, F. F., and Wilson, F. N.: The Ventricular Complex in Multiple Precordial Leads, Mod. Concepts of Cardiovasc. Dis. **12**: 1943.
5. Goldberger, E.: The Calculation of Axis Deviation in Unipolar Extremity Leads. To be published.
6. Fredericia, L. S.: Die Systolendauer in Elektrokardiogramm bei Normaler Menschen und bei Herzkranken, Acta med. Scandinav. **53**: 469, 1920.
7. Georgopoulus, M.: Über den Wert der Kontrolle der Digitalis Behandlung durch die Elektrokardiographie, Deutsches Arch. f. klin. Med. **176**: 348, 1934.
8. Larsen, K., Neukirch, F., and Nielsen, N. A.: Electrocardiographic Changes in Normal Adults Following Digitalis Administration, AM. HEART J. **13**: 163, 1937.
9. White, P. D., and Mudd, S. G.: Observations on the Effect of Various Factors on the Duration of the Electrical Systole of the Heart as Evidenced by the Length of the Q-T Interval of the Electrocardiogram, J. Clin. Investigation **7**: 387, 1929.
10. Pardee, H. E. B., and Cohen, A. E.: Clinical and Electrocardiographic Studies on the Action of Digitalis, J. A. M. A. **65**: 1527, 1915.
11. Pardee, H. E. B.: Rate of Absorption of Digitalis From the Gastro-Intestinal Tract, J. A. M. A. **75**: 1258, 1920.
12. Strauss, H., and Katz, L. N.: Effect of Digitalis on the Appearance of Lead IV, AM. HEART J. **10**: 546, 1935.
13. Pardee, H. E. B.: Clinical Aspects of the Electrocardiogram, New York, 1941, Paul B. Hoeber, Inc.

THE EFFECT OF CHRONIC CORONARY SINUS OCCLUSION ON THE VASCULARITY OF THE DOG'S MYOCARDIUM

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IN THE search for effective therapeutic measures against coronary disease, attention has turned in recent years to surgical procedures aimed at providing the heart with an additional blood supply from extracardiac sources.

In 1935, Gross and Blum[1] demonstrated by an injection and roentgenographic technique that occlusion of the coronary sinus produced an augmentation of the intrinsic arterial vascular bed. In dogs with previous coronary sinus occlusion, the incidence of infarction after ligation of the left anterior descending coronary artery was reduced.

Gross, Blum, and Silverman,[2] in subsequent experiments, found that the mortality after ligation of the left anterior descending coronary artery was reduced by previous partial coronary sinus occlusion, but not by total sinus occlusion. The size and frequency of infarction was reported to be diminished, and the arterial vascular bed enlarged, in hearts with partial sinus occlusion.

Electrocardiographic observations made after sinus occlusion yielded transient abnormalities which were ascribed by Gross and his co-workers[3] to myocardial ischemia due to venous congestion. The dilatation and cyanotic appearance of the left ventricle after obturation of the coronary sinus is in consonance with this view.

The experiments to be described were undertaken in order to ascertain whether or not the augmentation in the coronary arterial bed which has been noted within a period of several weeks after coronary sinus occlusion persists over a period of years.

METHODS

Adult mongrel dogs were anesthetized by giving nembutal intraperitoneally (25 mg. per kilogram). The surgical approach to the sinus was essentially that employed by Gross and his co-workers.[2, 4] Procaine solution, applied to the surface of the heart as described by Mautz,[5] eliminated cardiac irregularities produced by manipulation. A method of sinus closure was used which, it was hoped, would be gradual and progressive, and circumvent the effects of complete and sudden ligation. Although it was subsequently shown by Beck[6] that the high mortality after complete coronary sinus ligation in normal dogs observed by Gross[2] need not occur, this gives no assurance that a heart already impaired by coronary disease could survive the immediate deleterious effects of acute venous stasis.

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Accordingly, the coronary sinus was picked up gently in an Allis forceps at a point about 1 cm. from its entrance into the right atrium. A second Allis was then placed as completely around the sinus as possible. A small, c-shaped, metal clip, about 1/8 inch in width, and large enough in circumference to fit around the sinus and perisinus fat, was grasped in a Kocher's forceps and slipped around the vessel just at the side of the Allis forceps near the entrance of the sinus into the right atrium. The ends of the clip were serrated to prevent slipping. After being placed around the coronary sinus, the clip was compressed until the sinus beyond the clip just began to bulge. The pericardium and chest were then closed.

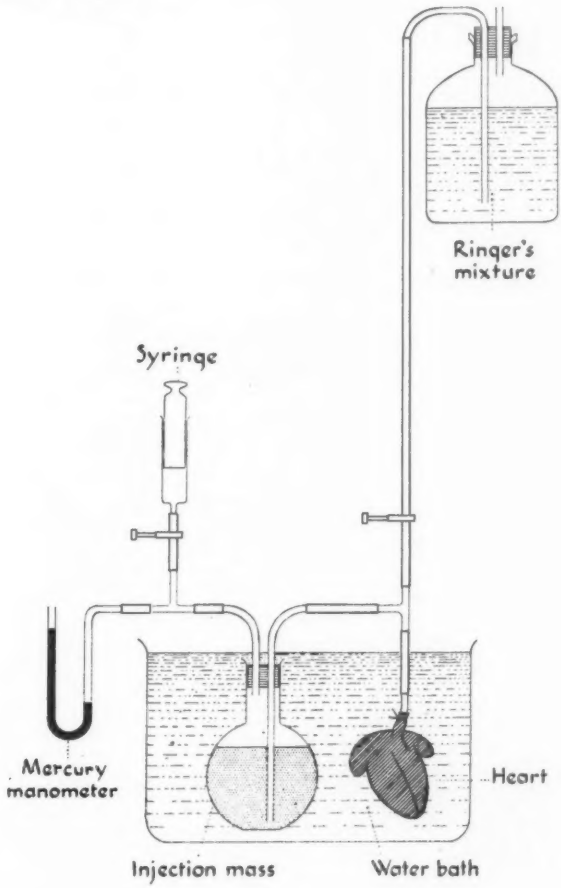

Fig. 1.

Six animals were prepared in this fashion. One died of a wound infection on the seventh postoperative day, and one of distemper on the twelfth day after operation. The other four survived, and were in good health when sacrificed three years later. The simplicity of the procedure is indicated by the absence of mortality due to the operation itself in the first six animals so treated.

After a period of three years, the animals were anesthetized with ether, and the hearts were excised widely in order to leave the atria in-

tact, and then injected, dissected, and roentgenographed in a manner essentially similar to that described by Schlesinger,[7] except for the injection. In the method used, the injection mass was introduced via the aorta, rather than the coronary arteries, for this was found to be simpler and more dependable; the right coronary artery frequently arises by multiple ostia, and is difficult to cannulate in the dog.

The aorta was cannulated under saline, care being taken to prevent the entrance of air into the system. The coronary arteries were then flushed with warm Ringer's fluid to remove the blood. After this, the heart was suspended in a saline bath at 45° C., the tube from the Ringer's fluid reservoir was clamped, and a side arm leading to the flask containing the injection mass was opened. The injection mass was then introduced as indicated in Fig. 1, in which a diagram of the method of injection is presented. A pressure of 150 mm. Hg was maintained during the injection and for a period of several minutes after the mass had ceased to move forward. Then the short segment of rubber tubing just above the aortic cannula was clamped and disconnected from the system, and, while pressure was still being maintained in the aorta, the heart was placed in the icebox until the injection mass had set. The procedure from this point forward was carried out as indicated.[7]

Nine control hearts were prepared in addition to the four experimentals.

Besides the roentgenograms, microscopic sections were made from the left ventricles of the control and experimental hearts, and the coronary sinuses in the experimental hearts were carefully dissected.

RESULTS

Of the four experimental hearts, only one showed a completely occluded sinus. The degree of closure was estimated at 30, 50, and 90 per cent in the other three hearts. In those with 30 and 50 per cent occlusion, the clips had not bent symmetrically on compression, and therefore did not completely surround the sinus. Although they occupied approximately the same position with relation to the vessel, there was an obvious difference in the degree of occlusion; this was probably accounted for by the difference in the material from which the clips were made. That on the more patent sinus had been made of silver, whereas all the others had been fashioned by cutting stainless skin clips down to size and bending them appropriately. This latter material apparently called forth a more marked connective tissue reaction than did the silver.

Thus, fortuitously, a series ranging from slight to complete closure of the coronary sinus was obtained. Examination of the roentgenograms of the injected specimens in no case showed augmentation of the arterial bed when compared with the controls. (In making the comparison, the number of small vessels visualized served as the criterion.) Indeed, the experimental specimens, as a group, appeared definitely less vascular than the controls, as a group, although there were less vascular hearts in the control group with which those which showed only partial

sinus occlusion compared favorably. This was not true, however, of the specimen with complete sinus occlusion, in which the least vascularity was demonstrated.

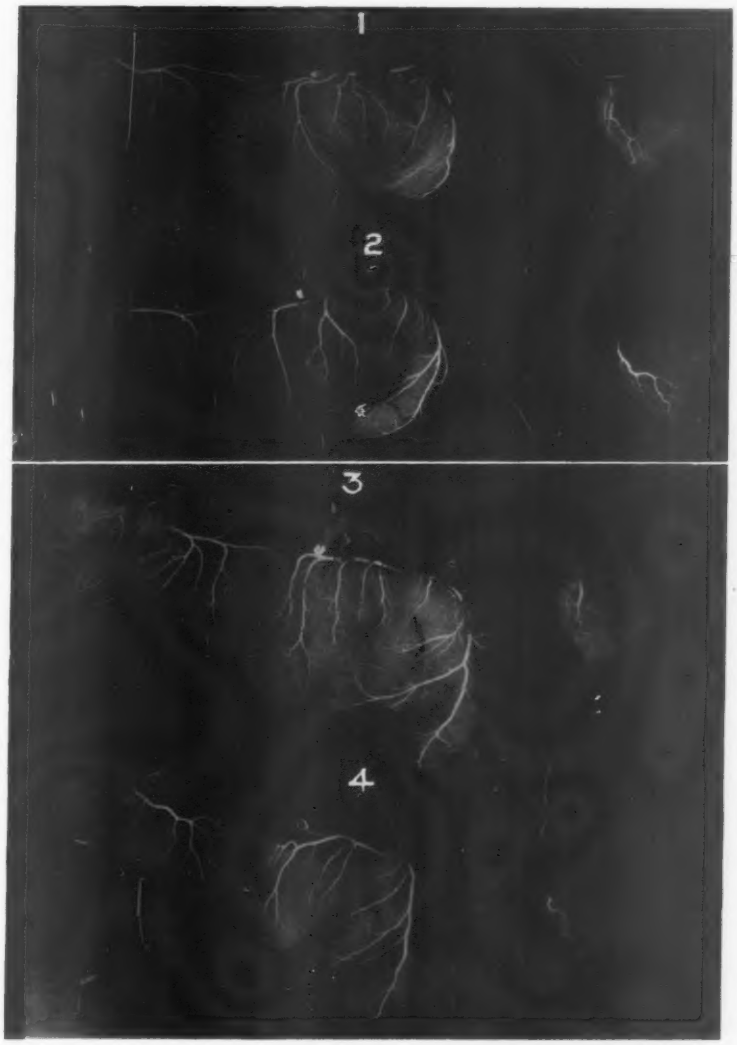

Fig. 2.

Within the experimental series itself, the vascularity appeared to vary inversely with the degree of obturation of the coronary sinus. Although the method, as a quantitative measure of the coronary bed, leaves much to be desired, and although it cannot be said with certainty that the differences here noted are not due to some unrecognized systematic discrepancy, there can be no doubt that so considerable an augmentation of the coronary arterial bed as that demonstrated by Gross,

et al.,[1, 2] after recent coronary sinus occlusion could not have been missed by this procedure, and certainly did not exist in these specimens.

Reproductions of the roentgenograms of the four experimental hearts and three of the controls are presented in Figs. 2 and 3. Observations on the experimental hearts are summarized in Table I.

TABLE I

HEART NUMBER	DEGREE OF SINUS OCCLUSION (%)	ROENTGENOGRAPHIC APPEARANCE OF VASCULAR BED	RELATIVE DENSITY OF THE VASCULAR BED*
1	50	Comparable to less vascular control hearts	+++
2	90	Comparable to less vascular control hearts	++
3	30	Comparable to moderately vascular control hearts	++++
4	100	Not as vascular as the least vascular control heart	+

*As compared to the other experimental hearts.

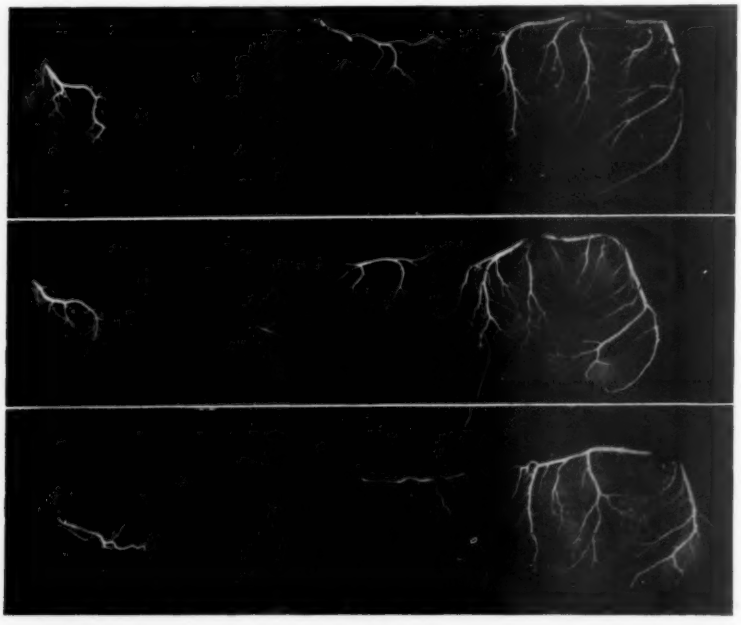

Fig. 3.

It may be observed that all the hearts shown in the figures (and this is true of all the specimens studied) are of the type with a predominant left coronary artery, previously described by Schlesinger[8] as typical in the dog.

Finally, it should be stated that careful study of the microscopic sections made from the control and experimental hearts showed no demonstrable differences.

DISCUSSION

Reports made available since the present study was undertaken lend some support to the observations just described. Gregg and his co-workers[9, 10, 11] have shown that the backflow from a ligated coronary artery peripheral to the point of ligation is considerably above the normal if the coronary sinus is ligated simultaneously. However, retrograde flow is only slightly increased if coronary sinus ligation is carried out thirty days prior to arterial occlusion. Sinus occlusion, however, was found to influence favorably the mortality from arterial occlusion.

Beck[6] also found a definite decrease in the mortality rate after coronary artery occlusion if the coronary sinus is also ligated. He reported, however, that the beneficial effect of venous ligation is least when vein and artery are closed at the same operation, that it is greatest when carried out six weeks prior to ligation of the artery, and decreases again when a longer interval (four months) elapses between the two procedures. Beck, unlike Gross, et al.,[1, 2] always found infarcts after arterial occlusion, but judged them to be smaller in size when sinus ligation had been done previously.

Obviously, before coronary sinus closure can be finally evaluated as a protective measure against arterial occlusion, the mortality, induced by the latter procedure when it is carried out one or more years after the former, must be ascertained.

The observations recorded to date lend slight support to the suggestion that coronary sinus occlusion might be of value as a therapeutic procedure in coronary disease by permanently increasing the basic vascular bed.

SUMMARY

Dog hearts, after three years of graded coronary sinus occlusion, varying from slight to complete closure, did not exhibit the augmentation of the coronary arterial bed which has been demonstrated by others within a period of days to weeks after obturation of this vessel. On the contrary, myocardial vascularity appeared reduced, if anything, as a result of this procedure.

REFERENCES

1. Gross, L., and Blum, L.: Effect of Coronary Artery Occlusion on Dog's Heart With Total Coronary Sinus Ligation, Proc. Soc. Exper. Biol. & Med. **32**: 1578, 1935.
2. Gross, L., Blum, L., and Silverman, G.: Experimental Attempts to Increase the Blood Supply to the Dog's Heart by Means of Coronary Sinus Occlusion, J. Exper. Med. **65**: 91, 1937.
3. Gross, L., Silverman, G., and Master, A. M.: Electrocardiographic Changes Following Coronary Sinus Occlusion in the Dog's Heart, AM. HEART J. **11**: 734, 1936.
4. Blum, L., and Gross, L.: Technic of Experimental Coronary Sinus Ligation, J. Thoracic Surg. **5**: 522, 1936.
5. Mautz, F. R.: Reduction of Cardiac Irritability by the Epicardial and Systemic Administration of Drugs as a Protection in Cardiac Surgery, J. Thoracic Surg. **5**: 612, 1936.

6. Beck, C. S.: Natural and Artificial Collateral Circulation in the Heart, Blood, Heart and Circulation, Lancaster, 1940, Science Press Printing Company, p. 133.
7. Schlesinger, M. J.: An Injection Plus Dissection Study of Coronary Artery Occlusions and Anastomoses, AM. HEART J. **15**: 528, 1938.
8. Schlesinger, M. J.: Significant Variations in the Anatomic Pattern of the Coronary Vessels, Blood, Heart, and Circulation, Lancaster, 1940, Science Press Printing Company, p. 61.
9. Gregg, D. E., and Dewald, D.: Immediate Effects of Coronary Sinus Ligation on Dynamics of Coronary Circulation, Proc. Soc. Exper. Biol. & Med. **39**: 202, 1938.
10. Gregg, D. E., and Dewald, D.: The Immediate Effects of the Occlusion of the Coronary Veins on Collateral Blood Flow in the Coronary Arteries, Am. J. Physiol. **124**: 435, 1938.
11. Thornton, J. J., and Gregg, D. E.: Effect of Chronic Cardiac Venous Occlusion on Coronary Arterial and Cardiac Venous Hemodynamics, Am. J. Physiol. **128**: 179, 1939.

PERICARDITIS ASSOCIATED WITH PRIMARY ATYPICAL PNEUMONIA

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A SURVEY of the admissions to the cardiovascular section of the Schick General Hospital has revealed a small group of cases of pericarditis which did not conform with any accepted etiologic classification. Upon reviewing these cases, it was found that all the patients had a concomitant or antecedent primary atypical pneumonia. A survey of the available literature revealed reports of isolated cases of pericarditis after upper respiratory infections,[1-3] but failed to disclose any report of pericarditis associated with primary atypical pneumonia. It was thought, therefore, that it would be of interest to report three such cases which have been under our observation.

CLINICAL COURSE

These three patients were men, and ranged in age from 19 to 27 years. Each illness began with an upper respiratory infection, characterized essentially by fever, sore throat, cough, and a variable degree of expectoration. Within a few days, when these patients appeared to have fully recovered, they suddenly developed an exacerbation of their symptoms, associated with pain in the anterior part of the chest which was aggravated by deep inspiration. In two of the cases, teleoroentgenograms taken at this time showed areas of pneumonitis interpreted as primary atypical pneumonia. The clinical course of the third patient was similar, but definite roentgenologic evidence of pneumonitis did not appear until six weeks later, although prominent hilar shadows and increased bronchovascular markings were present throughout this period. Roentgenologic evidence of pneumonitis persisted from twenty-seven to ninety-eight days. In all the cases, at some time during the course of the pneumonia, clinical signs of pulmonary disease, consisting primarily of moist râles over the involved areas, were detectable. As has been noted previously in primary atypical pneumonia,[4] the roentgenologic evidence of pneumonitis was more extensive than was suspected from clinical examination. At the onset of the pneumonitis a leucocytosis ranging from 15,000 to 18,000 was present in all three cases. The differential count was not remarkable. Blood cultures and typing of the sputum for pneumococci were negative in all the cases. Throat cultures failed to reveal any specific bacterial organisms. Urinalyses and Kahn tests were consistently negative. Sedimentation rates were not ascertained at this time.

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The interval between the onset of the upper respiratory infection and appearance of the pericarditis ranged from seven to forty-one days. The pericarditis was ushered in by an increase in the pulse rate in all cases from a previous level of 75 to 90 per minute to a range of 100 to 130 per minute, accompanied by a rise in temperature of 1.5° to 2° F. The respirations showed little change. In two cases a pericardial friction rub was audible at the onset; in one case the friction rub was audible for two days, and in the second case it was present for seven days. Typical electrocardiographic changes of acute pericarditis appeared simultaneously. In the other case no pericardial rub was detected and the diagnosis was made only by serial electrocardiograms. In the two cases in which a friction rub was audible, pain was present in the left anterior part of the chest, and, in one, this was associated with pain in the left shoulder. There was no significant alteration in the blood pressure during the course of the pericarditis. The clinical appearance of the patients during the period of pericarditis was variable. Two patients became apprehensive as the result of consciousness of a rapid heart rate. The remaining patient (J. H. B.) was more acutely ill and toxic. At no time were any of the patients in a critical condition.

The leucocytosis, which was present at the time of the pneumonitis, had begun to subside. With the onset of pericarditis, the leucocyte count increased from an average of 12,000 to 15,500. In two of the three cases, the sedimentation index was increased during the course of the pericarditis. At the onset of the pericarditis, the electrocardiogram in two of the three cases showed R-T elevations in the limb leads and Lead IV F which were consistent with the acute stage. In the third case no tracing was taken during the acute phase. The duration of this period varied from seven to fifteen days. In all three cases, the subacute pattern was present, which was characterized by T-wave inversion in some or all of the standard leads and Lead IV F. This subacute stage lasted from thirty-four to sixty-eight days. In all the cases, with the healing of the pericarditis, the R-T segments became isoelectric and the T waves, upright. Serial roentgenograms of the heart revealed enlargement of the cardiac silhouette in only one case. This amounted to 14 per cent, and it disappeared in twenty-seven days.

CASE REPORTS

CASE 1.—H. A. H., aged 19 years. The family and past history were noncontributory. On February 21, 1943, the patient was hospitalized with a sore throat, headache, cough, and chilliness. On admission his temperature was 102°, his pulse rate was 120, and the respiratory rate was 24. The pharyngeal structures were deeply injected. The remainder of the physical examination was not remarkable. He appeared to improve, but Feb. 27, 1943, he developed fever, pain in the chest, and cough, and roentgenologic studies at this time revealed patchy infiltration in the lower anterior part of the left upper lobe; this was interpreted as primary atypical pneumonia (Fig. 1). The leucocyte count

at this time was 14,000. Within three days the patient improved and became afebrile. On March 1, 1943, the patient again complained of pain in the left anterior part of the chest, and developed a temperature of 102.6° and a pulse rate of 110. A pericardial friction rub was audible at this time and persisted for two days. The temperature became normal in forty-eight hours. The leucocyte count rose to 16,350; the differential count was not remarkable. The electrocardiogram on March 1, 1943, revealed R-T elevation diagnostic of the acute stage of pericarditis (Fig. 2). This persisted until March 16, 1943, when the subacute stage, characterized by T-wave inversion in Leads I and IV F, appeared. The electrocardiogram returned to normal on April 19, 1943, giving a total duration of fifty days of graphic evidence of pericarditis. Roentgenologic evidence of the pneumonitis persisted until June 5, 1943, or a total of ninety-eight days. The sedimentation rate was elevated until May 20, 1943. Sputum examination for pneumococci, throat cultures for specific bacterial organisms, and blood cultures were negative.

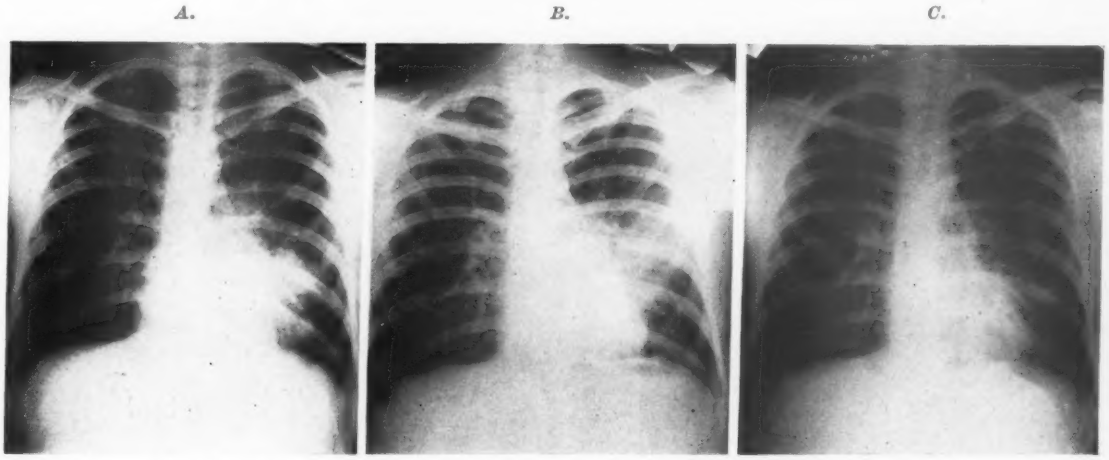

Fig. 1.—Case of H.A.H. *A*, Roentgenogram taken Feb. 28, 1943, illustrating infiltration of the left hilum and the lower portion of the left upper lobe. *B*, Roentgenogram taken March 16, 1943, illustrating further spread of the pneumonitis. *C*, Roentgenogram taken June 5, 1943, illustrating complete resolution of the pneumonic process.

CASE 2.—P. E. J., aged 27 years. The family and past history were noncontributory. On Feb. 10, 1943, this patient developed an upper respiratory infection. His symptoms persisted, and hospitalization was necessary on March 9, 1943. On admission his temperature was 104.2°, his pulse rate, 120, and his respiratory rate, 26. Except for injection of the pharynx, the physical examination was negative. A roentgenogram of the chest revealed patchy areas of pneumonitis in both lower lobes, more marked on the left; this was diagnosed as primary atypical pneumonia (Fig. 3). The leucocyte count was 18,300, with a normal differential. The patient appeared to improve, and, by March 18, 1943, he was afebrile and the leucocyte count had fallen to 11,650. On March 23, 1943, the pulse rate increased from a previous level of 90 to 120. Within twenty-four hours it rose to 140, and there was an associated rise in temperature from 98.6° to 100°. At the same time the patient complained of weakness and palpitation. He remained

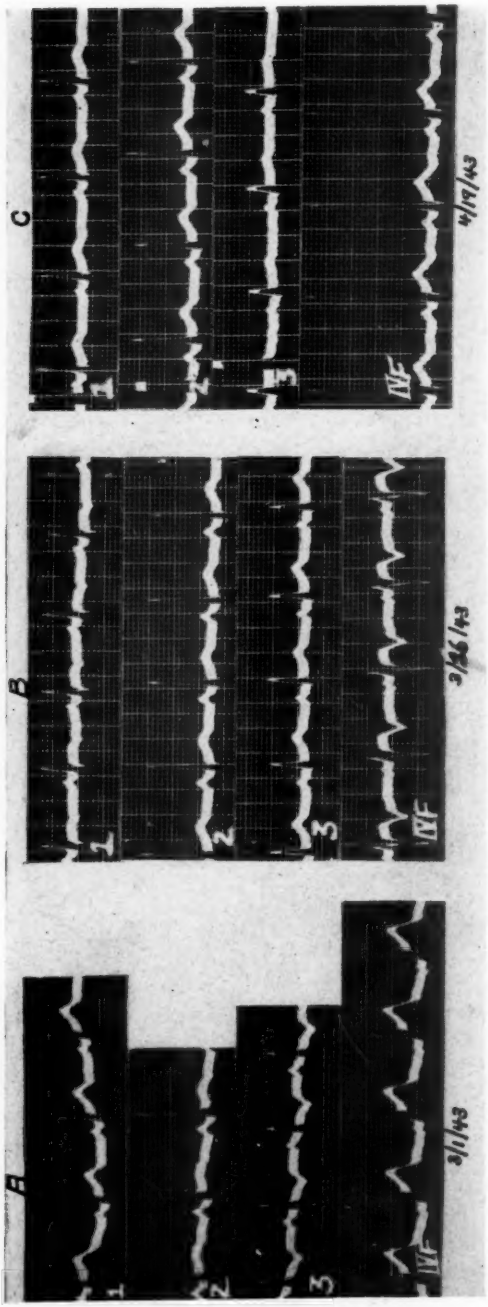

Fig. 2.—Case of H.A.H. *A*, ECG illustrating the onset of acute pericarditis; R-T elevation in Leads, I, II, and IV F. *B*, The subacute stage, with T-wave inversion in Leads I and IV F. *C*, The healed stage, with return of the ECG to normal.

febrile for four days. An electrocardiogram, taken March 30, 1943, showed inversion of the T waves in the standard leads and Lead IV F which was compatible with the diagnosis of pericarditis in the subacute stage (Fig. 4). The leucocyte count during this period rose to 15,650, and the sedimentation index was increased. Electrocardiograms were taken at frequent intervals, and did not become normal until June 7, 1943, making a total of sixty-eight days of electrocardiographic evidence of pericarditis. At no time during the illness was a pericardial friction rub audible. Roentgenologic evidence of pneumonitis persisted for twenty-seven days. Sputum examination for pneumococci, throat cultures for specific bacterial organisms. and blood cultures were negative.

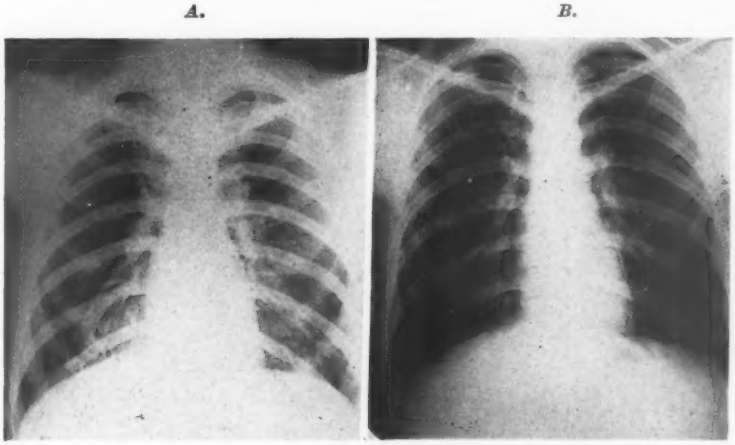

Fig. 3.—Case of P.E.J. *A*, Roentgenogram taken March 22, 1943, illustrating areas of pneumonitis in both lower lobes, more marked on the left. *B*, Roentgenogram taken in April, 1943, illustrating complete resolution of the pneumonic process.

Case 3.—J. H. B., aged 27 years. The family and past history were noncontributory. On April 5, 1943, the patient was hospitalized because of mumps. One week later, while his symptoms and signs were subsiding, he developed cough, with expectoration of mucus, associated with a sharp rise in temperature to 102°. The pulse rate was 100 and the respiratory rate was 22. Physical examination was negative except for an injected pharynx. The leucocyte count at this time was 13,850. On April 19, 1943, he complained of severe substernal pain aggravated by deep inspiration and accompanied by pain in the left shoulder. At this time a pericardial friction rub was audible and persisted for one week. The temperature rose from a previous level of 101° to 103.8°, and the pulse rate increased from 65 to 105. The leucocyte count rose to 16,450, and the sedimentation index was normal. The electrocardiogram on April 20, 1943, revealed R-T elevation in Leads I, II, III, and IV F which was consistent with the acute stage of pericarditis (Fig. 5). A chest roentgenogram did not show any definite evidence of pneumonitis at this time. The electrocardiogram showed abnormalities characteristic of pericarditis until July 6, 1943, making a total duration of seventy-nine days for the period of pericarditis. Frequent roentgenograms of the chest were taken, and, although the hilar markings showed increased prominence, definite pneumonitis was not apparent until June 6, 1943 (Fig. 6). Roentgenologic evidence of pneumonitis persisted until

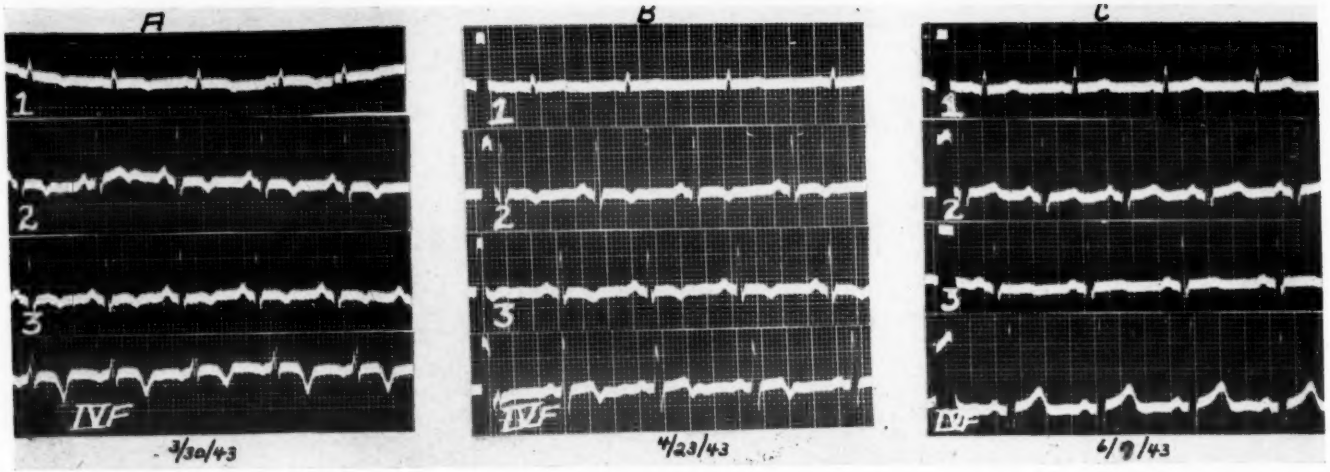

Fig. 4.—Case of P.E.J. *A*, ECG one week after onset of acute pericarditis, showing T-wave inversion in all leads. *B*, ECG illustrating healing. The T wave in Lead I has become upright and the T wave in Lead IV F has become diphasic. *C*, ECG showing the healed stage, with return to normal.

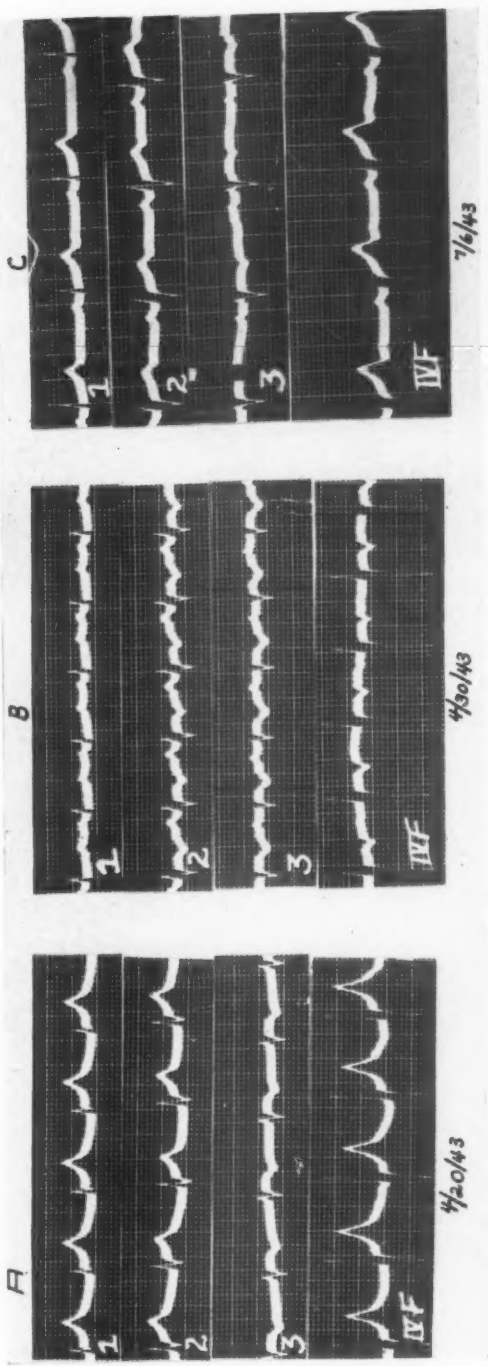

Fig. 5.—Case of J.H.B. *A*, ECG illustrating the onset of acute pericarditis; R-T elevation in all leads. The terminal portion of the T wave in Lead III shows early inversion. There is low voltage in the standard leads. *B*, The subacute stage, with T-wave inversion in Leads II, III, and IV F. *C*, The healed stage, with return of the RS-T segments and T waves to normal.

Aug. 5, 1943, or a total of sixty days. Sputum examinations for pneumococci, throat cultures for specific bacterial organisms, and blood cultures were negative.

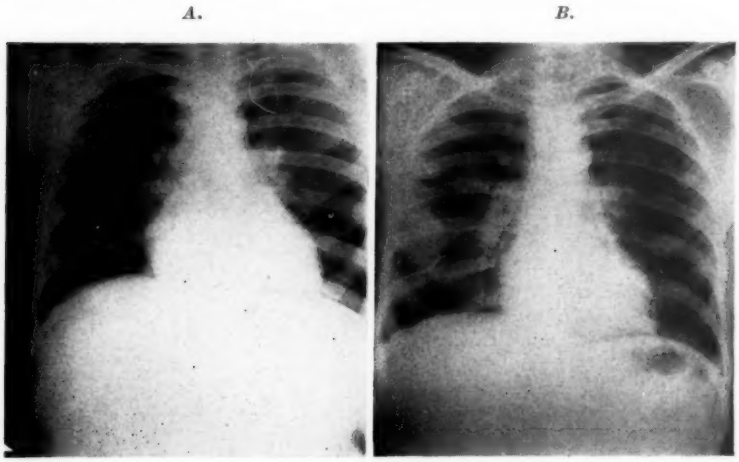

Fig. 6.—Case of J.H.B. *A*, Roentgenogram taken April 20, 1943, illustrating increased bronchovascular markings in the right hilar area. *B*, Roentgenogram taken June 12, 1943, illustrating pneumonitis in the hilar region and the periphery of the right lung.

DISCUSSION

It is thus apparent that pericarditis may occur in association with primary, atypical pneumonia. Clinically these patients present a paucity of symptoms and signs, and the diagnosis depends in large measure on changes in the electrocardiogram. A pericardial friction rub, which is diagnostic, may be present but may not be detected unless the patient is seen and examined at very frequent intervals. It is probable that additional cases would be uncovered if serial electrocardiograms were taken in all cases of primary atypical pneumonia. This condition should be suspected if, during the course of the pneumonia, there is an unexplainable rise in temperature, associated with tachycardia, or if the patient is running an unduly protracted course.

It is probable that the etiologic agent responsible for the atypical primary pneumonia is also the cause of the associated pericarditis. Throat cultures, sputum examinations and typing, and blood cultures did not reveal any specific bacterial organisms. Studies were carried out at the Army Medical Museum on blood samples from these patients to ascertain whether the virus of psittacosis, Q fever, or lymphocytic choriomeningitis was present. The results were negative. The presence of a pericardial friction rub in two of these cases and the absence of clinical or roentgenologic evidence of pericardial effusion suggest that the pericarditis was fibrinous in nature. Although in one case the cardiac silhouette, as visualized roentgenographically, did increase in size, its configuration and the symptoms and signs did not suggest pericardial effusion.

Pericarditis is usually secondary to other diseases, particularly pulmonary and cardiac diseases.[5] The pericardium may become involved either by direct extension, by lymphatic or hematogenous spread, or by chemical alterations of the blood. In this group of cases, the roentgenograms of the chest consistently revealed increased bronchovascular markings in the hilar region, radiating to the periphery. Furthermore, the pneumonitis developed on the side in which the bronchovascular markings were increased. In the absence of positive blood cultures and chemical alteration of the blood, it appears that the pericardium became involved secondarily, either by direct extension or by lymphatic spread. All of these patients recovered fully, and, at the time of discharge, there was no clinical, roentgenologic, or electrocardiographic evidence of pericardial disease. Not enough time has elapsed to definitely exclude pericardial adhesions as a complication.

Although the problem of different diagnosis was not difficult in these cases, it is conceivable that at times it would be difficult to rule out rheumatic pericarditis. This is particularly true of rheumatic pericarditis which develops in complete absence of migratory polyarthritis, follows an upper respiratory infection, and is accompanied by signs of pneumonitis. In contrast to the reported cases, the patients with rheumatic pericarditis are more acutely ill, the pneumonitis is evanescent, both clinically and roentgenologically,[6] and a cardiac murmur is usually present. The electrocardiographic changes caused by the pericarditis may be similar in the two diseases, but with rheumatic pericarditis there may be associated alterations in the P waves, prolongation of the P-R interval, and disturbances of rhythm. Patients with rheumatic pericarditis have a more protracted course and require a longer period of rest in bed. Not infrequently they develop permanent endocardial lesions. In one of our cases a harsh systolic murmur developed at the base of the heart during the course of the pericarditis. During convalescence, however, this murmur became less intense and ultimately disappeared. None of our patients developed valvular heart disease. Other types of pericarditis associated with pulmonary disease, such as tuberculous and pyogenic pericarditis, usually do not present any difficulty in differential diagnosis.

All of these patients received short courses of sulfonamide therapy without any apparent benefit. Treatment otherwise was entirely symtomatic, and the disease appeared to run its own course. Rest in bed was maintained until the sedimentation rate and leucocyte count became normal, complete resolution took place in the lungs, and the electrocardiogram returned to normal.

SUMMARY

1. Three cases of pericarditis associated with primary atypical pneumonia are presented.

2. The diagnosis can be made either by the presence of a pericardial friction rub or, more commonly, by typical electrocardiographic changes. It should be suspected if, during the course of the pneumonia, an unexplainable rise in temperature, associated with tachycardia, develops, or if the illness is running an unduly protracted course.

3. The cause of the pericarditis has not been established, but is probably identical with that of the primary atypical pneumonia.

4. Prognosis as to life is good, and, at the end of the hospital stay, no evidence of pericardial disease could be demonstrated.

REFERENCES

1. Willius, F. A.: Clinic on Acute Serofibrinous Pericarditis Secondary to Acute Pharyngitis; Comment; Treatment; Course, Proc. Staff Meet., Mayo Clin. **9**: 637, 1934.
2. Comer, M. C.: Acute Pericarditis With Effusion. A Sequel to Sinusitis, Southwestern Med. **11**: 310, 1927.
3. Bellet, S., and Finkelstein, D.: Unpublished data.
4. Dingle, J. H., et al.: Primary Atypical Pneumonia, Etiology Unknown, War Med. **3**: 223, 1943.
5. White, Paul D.: Heart Disease, New York, 1942, The Macmillan Company.
6. Gouley, B. A.: The Acute and Subacute Pulmonary Involvement in Rheumatic Fever With Notes on the Complication of Basal Pulmonary Collapse, Ann. Int. Med. **11**: 626, 1937.

Clinical Reports

COR BIATRIATUM TRILOCULARE

Case Report

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COMPLETE absence of the ventricular septum, resulting in the three-chambered heart, is a rare cardiac anomaly. In Abbott's[1] statistical analysis of 1,000 cases of congenital cardiac disease, thirteen cases are reported in which cor-biatriatum triloculare is classified as the primary lesion. In fourteen additional cases, it was found complicating other defects, making the total incidence 2.7 per cent of all that particular series of congenital cardiac abnormalities. The present case report concerns this unusual anomaly occuring as a primary defect.

CASE REPORT

A 9-year-old white boy was admitted to the Massachusetts General Hospital Jan. 26, 1933, because of "heart trouble." His birth was reported as spontaneous at term, and there was no cyanosis. He had always been slightly underweight, but was not a sickly child. He had mumps at the age of 4 years, and measles at 5 years. Both were mild. He had had few sore throats, although his tonsils were said to be enlarged by the school physician. There had been no joint pains or nosebleeds, but he had complained of pain in the calves of his legs that awakened him at night. There was a history of nightmares from which he awakened screaming. His family history was not remarkable except that his father gave a history of rheumatic fever at the age of 16 years, without recurrences.

Two years before entry, a school physician had informed his family that he had heart disease. His mother attempted to limit his activity, but without much success. There was no history of cyanosis on effort or on ordinary exposure to cold, but he did get quite blue when in swimming, even for a short time. He puffed a little more than his siblings when climbing stairs, but had always been very active. He raced and played football and baseball about as well as his playmates. Three weeks before admission, he had a dry cough and diarrhea, and became dyspneic even in a sitting position. There was no swelling of the legs, face, ankles, or hands. His urine was reported as dark, reddish-brown in color for a period of several days, and then appeared cloudy for about one week. On the day of admission. he complained of pain in the right ankle. There was no swelling or redness. His local physi-

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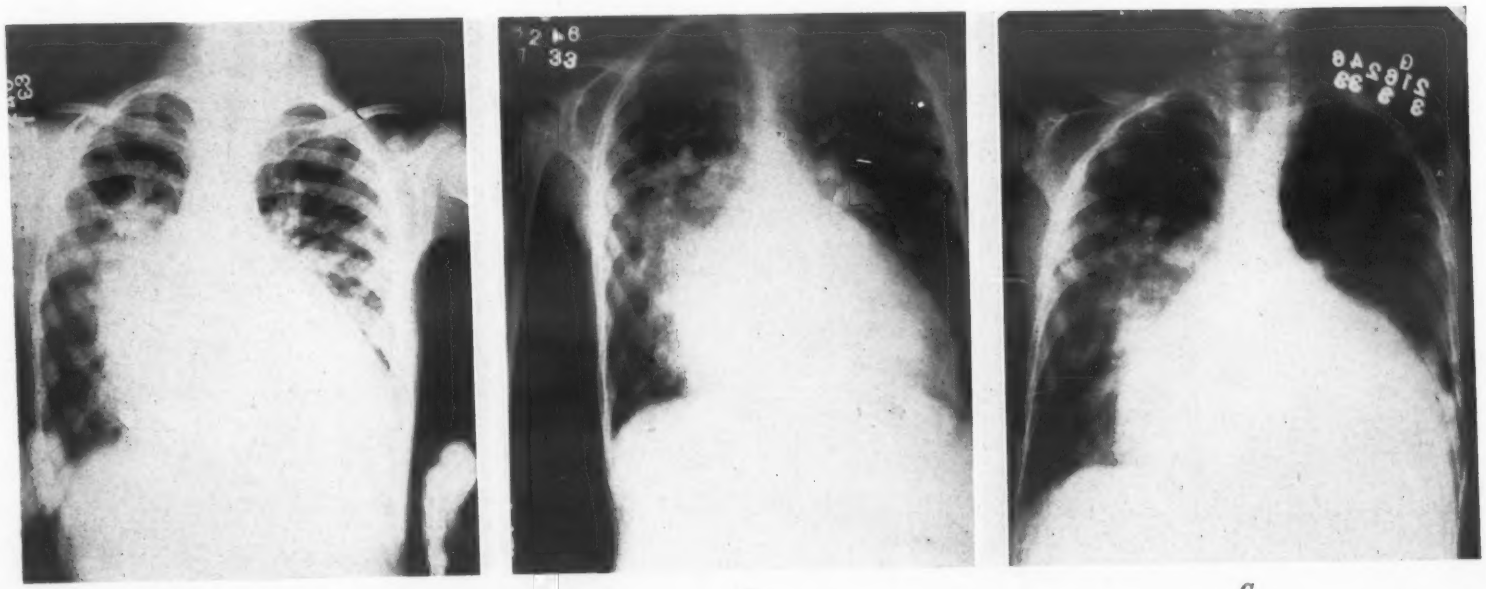
cian put him to bed because his heart was enlarged. He had taken tincture of digitalis for nearly three weeks.

Physical examination showed a very ill, pallid boy with shadows and slight puffiness under the eyes and a fine perspiration over the whole body. He had a frequent, hacking cough. The tonsils were moderately enlarged and slightly red, and small cervical lymph nodes were palpable bilaterally. The chest showed marked deformity. There was a bulging asymmetry, with protrusion of the ribs at the costochondral junction on the left, which seemed wider than on the right. There was some flaring of the ribs. A visible, diffuse, heaving impulse was present over the whole left side of the chest, part of the right side of the chest, and in the epigastrium. The left border of cardiac dullness in the fifth intercostal space measured 7½ cm. from the midline, constituting definite cardiac enlargement, and the right border of dullness was also definitely increased. A loud, systolic murmur was heard over the entire precordium and also in the back, but maximally at the cardiac apex. A mid-diastolic murmur was also heard at the apex. An inconstant "friction rub" was heard in the fourth intercostal space about 4 cm. to the left of midsternum. The heart rhythm was regular except for an occasional premature beat. The blood pressure measured 86/68. There was some fullness of the neck vessels. Examination of the lungs revealed some dullness at the left base, behind the heart, in which location a few subcrepitant râles were heard. Larger, moist râles were heard over both bases posteriorly. The liver was palpable four fingerbreadths below the costal margin, and was slightly tender. The spleen was not felt. There were no rheumatic nodules. There was no clubbing of the fingers and little, if any, cyanosis. At the time of admission, the temperature was 99.6° F., the pulse rate, 130, and the respiratory rate, 40.

The laboratory findings were as follows: The initial leucocyte count was 17,650, with 76 per cent polymorphonuclears. The hemoglobin measured 80 per cent (Tallquist). The urine at the time of admission contained many erythrocytes and occasionally leucocytes, but no erythrocytes were found in subsequent specimens. No casts were seen. One blood culture was reported negative. A roentgenogram of the chest, taken on the second hospital day, was reported as follows: "All measurements of the heart are greatly increased. The heart is rounded in shape and there is extreme prominence of the left auricle in both the antero-posterior and oblique views. The hilus shadows show marked increase in density, particularly on the right, extending well out into the lung fields. The periphery of the lung fields is clear. The appearance is consistent with rheumatic heart disease with multiple valve lesions and chronic passive congestion of the lungs. Also consistent with congenital heart disease." (See Fig. 1, *A*). Ten days later a second roentgenogram was reported as showing no change. However, careful scrutiny does reveal abnormalities of diagnostic importance (Fig. 1, *B*). The electrocardiogram four days after admission showed sinoauricular tachycardia, a pulse rate of 120, increased voltage, a P-R interval of 0.18 second (somewhat increased for his age), definitely prolonged QRS complexes consistent with intraventricular block, and slight right axis deviation (Fig. 2). No further tracings were made.

Clinical Course.—The temperature remained elevated on the day of admission and rose to 103.8° F. The following day the variation was from 97° to 102° F., and thereafter it varied between 97 and 100.5° F. Treatment consisted of 15 to 30 grains of aspirin daily and supportive



A. *B.* *C.*

Fig. 1.—*A*, Taken on the day after admission to hospital. The heart is greatly enlarged in all diameters, and there is extensive pulmonary vascular engorgement. Note the marked density and the width of the supracardiac shadow. *B*, Twelfth hospital day. Some improvement in the pulmonary vascular congestion. Supracardiac shadow less dense. Note the decreased width of the great vessels and absence of aortic knob. *C*, Thirty-sixth hospital day, just before death. Cardiac silhouette appears to have increased somewhat in size, and the contour is more bottle-shaped, suggesting pericardial effusion.

measures. For three weeks he showed some improvement. However, orthopnea continued and he found greatest comfort with a high back rest and his knees drawn up. The friction rub heard at the time of admission disappeared. On the seventeenth hospital day, he developed a severe coughing spell and grew more pallid, and, on examination, the heart was found to have increased in size. The leucocyte count at this time was 15,500, and later rose to 28,000 on the thirty-third hospital day. He became gradually worse and began to vomit much of his food.

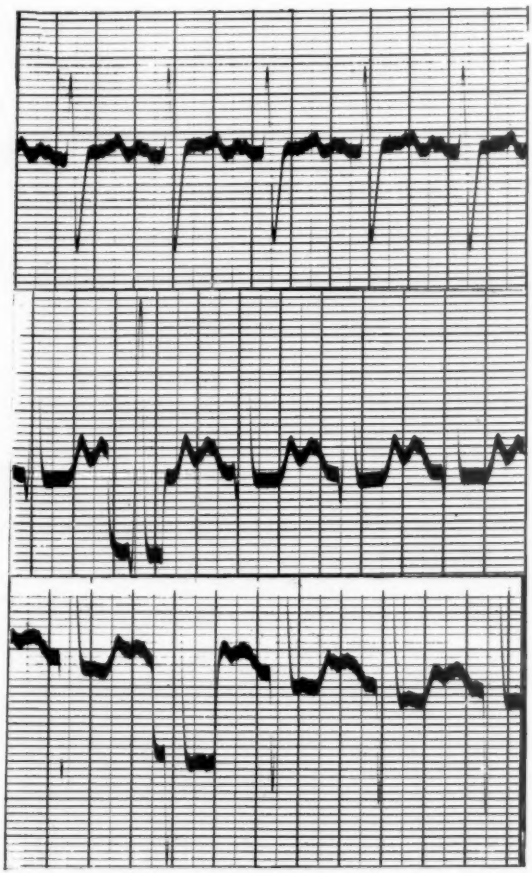


Fig. 2.—Electrocardiogram taken on fifth hospital day. Note sinoauricular tachycardia, pulse rate, 120, slightly prolonged P-R interval (0.18 second), and definite prolongation of intraventricular conduction time (0.12 second), also increased amplitude of QRS complexes.. The tendency is to right axis deviation.

Morphine was necessary to induce sleep. The heart appeared to enlarge to such an extent that pericardial effusion was suspected, and, on the thirty-six hospital day, a tap was attempted, but only dark blood was obtained. He died the following morning, March 4, 1933. There was only slight terminal cyanosis. A final roentgenogram of his chest on the day before he died was reported as showing little change except for some evidence of pulmonary atelectasis or fluid at the left base (Fig. 1, *C*). A clinical diagnosis of acute and chronic rheumatic heart disease, with acute cardiac dilatation and failure, was made.

PERTINENT AUTOPSY OBSERVATIONS

Autopsy revealed a well-developed and well-nourished boy of 9 years, weighing about 70 pounds. who showed a bulging precordium with four puncture marks in the skin. The liver was enlarged, and lay entirely below the costal margin. The two halves of the diaphragm were at the eighth rib. There was partial collapse of both lungs, but no pneumonia was seen. The pericardium was filled with 750 c.c. of unclotted blood. The heart was estimated to weigh about 600 grams. At the apex of the heart, on its anterior surface, two small puncture wounds were seen,

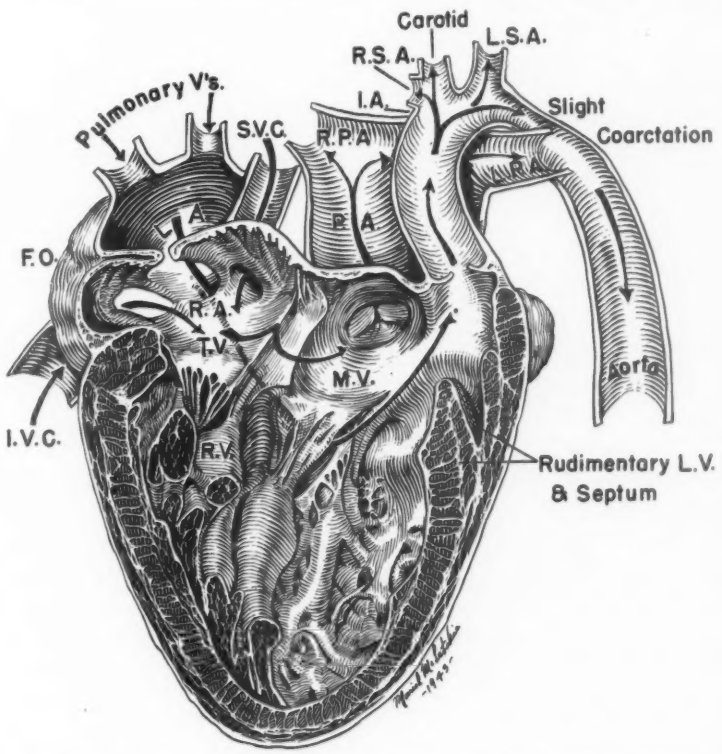


Fig. 3.—Schematic drawing of heart, laid open, showing large, common (right) ventricle and small rudimentary left ventricle. Note relatively small, coarctated aorta and large dilated pulmonary artery. *M.V.*—mitral valve, *T.V.*—tricuspid valve, *R.A.*—right auricle, *I.V.C.*—inferior vena cava, *F.O.*—foramen ovale (patent), *L.A.*—left auricle, *S.V.C.*—superior vena cava, *P.A.*—pulmonary artery. *R.P. A.*—right pulmonary artery, *L.P.A.*—left pulmonary artery, *I.A.*—innominate artery, *L.S.A.*—left subclavian artery.

around which there was a small amount of fibrin and hemorrhage into the muscle. Two other puncture wounds were found in the region of the right auricular appendage, covered by a recent, adherent, greyish-red, ante-mortem thrombus. The heart was very large, and the ventricular wall measured 22 mm. in thickness. The superior and inferior venae cavae entered the right auricle in normal fashion, and a patent foramen ovale, 1 cm. in diameter, was present. The left auricle received the pulmonary veins normally. There was one large ventricular cavity, with a very small outpocketing which doubtless represented the rudimentary left ventricle or bulbus. From the large ventricular cavity

the aorta arose at the anterior upper left margin. The base of the aorta formed the definite bulb just mentioned. This bulb was seen to be made up of a small chamber about 3 cm. in diameter, partially separated by a ridge of tissue (rudimentary septum) from the large, essentially common ventricle (Fig. 3). The aorta measured 2 cm. in diameter at its site of origin. The relationship of the pulmonary artery to the aorta was that which would be present in a normal heart if it failed to rotate to the left. The valves were not opened and measured, but, on inspection, all but the mitral valve seemed smooth and competent. The mitral valve was thickened along its free border, but no vegetations were present. The coronary arteries were normal in origin. The diameter of the dilated pulmonary artery was several times that of the aorta. Just past the site of origin of the left subclavian artery, the aorta was slightly to moderately coarctated, and measured 8 mm. in diameter at this point. Also at this point, the aorta appeared to take an angular bend, and became the descending aorta, measuring 1.8 cm. in diameter. The ductus arteriosus left a small dimple in both the pulmonary artery and the aorta. It measured 8 mm. in diameter, and, on cut section, a pin-point lumen remained. The anatomic diagnoses were as follows: Cor biatriatum triloculare, with rudimentary left ventricle; cardiac hypertrophy and dilatation; congestive heart failure; patent foramen ovale; slight coarctation of the aorta; puncture wounds of the heart; hemopericardium; and pulmonary congestion and atelectasis.

DISCUSSION

The clinical features of this case are unusual. Congenital cardiovascular defects with this degree of venoarterial communication are, with few exceptions, attended by at least a moderate degree of cyanosis, which was not clearly present in this patient even in his final illness. The fact that physical disability among congenital cardiacs may be more or less directly proportional to the degree of cyanosis most probably explains the history concerning his physical activity. Nevertheless, despite the benign early history, he survived only by one year, or so, the mean age (7¾ years), as given by Abbott[1] in thirteen cases of this malady.

Consideration of the pathologic anatomy suggests an explanation for the absence of cyanosis. First, the location of the aorta was such that the arterial blood returning via the mitral valve doubtless formed a barrier against too great admixture with venous blood returning via the tricuspid valve, as is apparently the case in the three-chambered turtle's heart. If this assumption is correct, the blood leaving the heart through the aorta must have been very predominantly arterial. Secondly, the great size of the pulmonary artery, as compared to the aorta, served the process of oxygenation of the blood well until dilatation and failure of the heart made this no longer possible. The part played by coarctation of the aorta in bringing about the final break is problematical; it does not seem likely that it was of any real importance. No blood pressure readings were made prior to his hospital entry, and those made after admission did not suggest coarctation. Also, no characteristic notching of the ribs was seen in the chest roentgenograms.

Each observer who saw this patient concurred in the diagnosis of rheumatic heart disease with mitral involvement, and interpreted the febrile illness as an active rheumatic infection, which indeed it may have been, although no microscopic evidence of this was found in the myocardium. The presumably acquired heart disease discovered at the age of 7 years, the joint pain, fever, leucocytosis, enlarged heart, murmurs, precordial friction rub, and later the apparently enlarging cardiac silhouette, suggesting pericardial effusion, altogether favored this conclusion. In reviewing the available objective clinical evidence there are two important indications of congenital heart disease that were overlooked, namely, the delay in intraventricular conduction time, and extensive excursions of the QRS waves, as shown by the electrocardiogram (Fig. 2), and the definitely abnormal supracardiac (aortic) shadow in the roentgenogram (Fig. 1). The reasons for both were at once apparent at the post-mortem table. There was no septum to carry the bundle branches in a normal fashion, and the aorta was hypoplastic and abnormally situated. In view of our present knowledge, the apical systolic and diastolic murmurs were most likely produced by a dilated (insufficient), relatively stenotic, mitral ring opening into a markedly dilated ventricular cavity. It is unlikely that the loud, widely transmitted systolic murmur arose from the site of slight coaretation in the aorta. The unfortunate result of the attempted pericardial taps re-emphasizes the difficulty that sometimes attends the differential diagnosis of pericardial effusion and cardiac dilatation, and illustrates the possible danger of paracentesis in this region. Whatever pericardial effusion may have been present was obscured at autopsy by the extensive hemopericardium.

SUMMARY

A case of three-chambered heart (cor biatriatum triloculare), with a tiny, rudimentary left ventricular pocket, attended by slight coaretation of the aorta in a boy aged 9 years is reported. The unusual clinical features, namely, absence of cyanosis and relatively good cardiac reserve until shortly before death, are discussed. The congenital abnormalities were complicated by a terminal infection (? rheumatic) and rapid dilatation and failure of the heart. The clinical diagnosis of chronic rheumatic heart disease, with mitral involvement was incorrect.

REFERENCE

1. Abbott, Maude E.: Atlas of Congenital Cardiac Disease, New York, 1936, Am. Heart Assoc.

Abstracts and Reviews

Selected Abstracts

Green, H. D., Lewis, R. N., Nickerson, N. D., and Heller, A. L.: Blood Flow, Peripheral Resistance, and Vascular Tonus, With Observations on the Relationship Between Blood Flow and Cutaneous Temperature. Am. J. Physiol. 141: 518, 1944.

Vascular tonus is defined as the active contraction of the muscular walls of the small blood vessels and is considered to be influenced, physiologically, by vasomotor nerve impulses, humoral substances, and metabolic products. The summated effects of the first two are defined as the vasomotor activity. Changes in vascular lumen in response to altered intraluminal pressure, per se, are considered to be a physical reaction and not to represent a change in vascular tonus.

The relationship between vasomotor activity, peripheral resistance, blood flow, and subcutaneous temperature was studied by recording either the arterial inflow or the venous outflow at a series of perfusion pressures in various vascular beds in the hind limbs of anesthetized dogs. These studies were made during control states, during periods of increased vasomotor activity occurring spontaneously and induced by small hemorrhages, and during periods of decreased vasomotor activity induced by sectioning the sciatic nerve. Average blood flow, at mean arterial pressure, was 6.9 ml. per 100 Gm. of muscle. In the combined skin and muscle of the lower half of the hind extremity, the average flow was 3.2 ml. per 100 grams of extremity, and, in the skin of the latter, the average flow was 1.6 ml. per 100 grams of extremity.

Only experiments in which the hematocrit reading and viscosity of the blood remained within +4 to –6 per cent of the control values and in which collateral circulation artifacts were avoided were analyzed. During a constant state of vasomotor activity the increments of blood flow per increment of perfusion pressure in skin and often in muscle increased regularly from zero upward when flow was measured immediately after establishment of the perfusion pressure. The relationship between perfusion pressure and flow in these experiments could be represented by the equation $F = \frac{P^n}{C}$, where n has values between 1 and 5, usually about 2. This relationship appears to be explainable on a purely physical basis. When the rate of flow was measured one to two minutes after establishment of the perfusion pressure in muscle and in the whole distal part of the extremity, the flows at pressure below mean arterial pressure appeared to be relatively greater than they would be on the basis of a purely physical relationship between pressure and flow. This was probably due to a vasodilatation induced locally by the accumulation of metabolic products as a result of the slowed flow at low perfusion pressures, but might also be due to a lowering of the extravascular pressure. The result was a sigmoid rather than a parabolic shaped curve relating perfusion pressure and flow.

In all experiments, increase of vasomotor activity decreased the rate of flow at each perfusion pressure. In those experiments in which the data fitted the equation $F = \frac{P^n}{C}$, increase of vasomotor activity increased the magnitude of the constant C and of the exponent n.

Peripheral resistance, physically, is the ratio of the perfusion pressure to the flow through the vascular bed. The term *PRU* is proposed as a unit of peripheral resistance, where 1 PRU $= \frac{1 \text{ mm.Hg}}{1 \text{ ml./min.}}$. Peripheral resistance was found to be altered when the perfusion pressure was raised or lowered, even when vasomotor activity remained constant. Conversely, change of vasomotor activity was not, in all cases, correctly indicated by an appropriate alteration of peripheral resistance.

Various methods of expressing change of vasomotor activity were discussed. It was concluded that the only completely satisfactory method is to compare the plot relating pressure to flow over the complete range of pressures from zero to mean aortic pressure in a control period, with a similar plot obtained in the experimental period. However, this method is laborious, and it is difficult to depict the progressive changes in these plots with time. As a compromise the next most satisfactory method appears to be to determine, during a control period, the relationship between pressure and flow over the entire range of flows anticipated during the subsequent experimental period, and thereafter to make only single determinations of pressure and flow, usually at a perfusion pressure equal to the existing mean aortic pressure. The results may then be expressed in terms of the ratio of the peripheral resistance (or perfusion pressure) in the experimental period to the peripheral resistance (or perfusion pressure) observed during the control period at the same rate of flow.

AUTHORS.

Corcoran, A. C., Taylor, R. D., and Page, I. H.: Immediate Effects on Renal Function of the Onset of Shock Due to Partially Occluding Limb Tourniquets. Ann. Surg. **118**: 871, 1943.

The depression of renal function during the onset of shock due to partially occluding tourniquets is due to a decrease of renal blood flow, which is only in a minor and inconstant measure the result of decreased arterial pressure.

This decrease of renal blood flow is due, almost wholly, to increased renal vascular resistance, in which increased blood viscosity enters only in a small degree; the increased resistance being rather due to vasoconstriction, predominantly affecting the glomerular efferent arterioles.

Although nervous stimulation, presumably as the result of pain, causes a small measure of this vasoconstriction, the larger fraction is independent of the renal nerves and, by exclusion, of humoral origin.

This humorally-arising renal vasoconstriction is associated with the appearance of a vasoconstrictor substance in plasma, to the activity of which it is therefore attributed.

AUTHORS.

McMichael, J., and Sharpey-Schafer, E. P.: Cardiac Output in Man by a Direct Fick Method. Brit. Heart J. **6**: 33, 1944.

Serial estimations of cardiac output and right auricular pressure can be made by means of a ureteric catheter passed along the veins into the right auricle.

Normal resting values for arteriovenous oxygen differences were rather lower than those obtained previously by the acetylene method.

Cardiac output in the supine posture showed a 33 per cent increase over that in the erect.

A fall in right auricular pressure reduced, and a rise in right auricular pressure increased, the cardiac output.

Acceleration of the heart with atropine usually increased cardiac output and caused a fall in right auricular pressure. Occasionally the fall in right auricular pressure may operate against an increase in cardiac output.

Intravenous adrenalin, in doses that did not accelerate the heart or raise the blood pressure increased cardiac output.

Normal subjects with high resting outputs had faster heart rates than the others.

AUTHORS.

Dawson, G. D., and Jones, A. M.: Synchronous Heart Sound Recordings. Brit. Heart J. 6: 48, 1944.

A method of synchronous heart sound recording is described in which the standard Cossor-Robertson cardiograph is modified by introducing a second channel, using the Clothier electronic switch.

Synchronization of the tracings is automatic and requires no adjustment.

The alteration to the commercial instrument is simple and does not affect its use as a simple portable cardiograph.

AUTHORS.

Stern, V. S.: Stokes-Adams Attacks in a Child. Brit. Heart J. 6: 66, 1944.

A case of insidious rheumatic pericardial effusion with Stokes-Adams attacks is described. A boy of 12 years sought medical help after three months of ill health, and only when disturbance of the conducting system had set in. Either minor inflammation of the bundle tissue itself or its compression by inflammatory vascularization of the collagenous mass in the septum membranaceum, would explain the symptoms.

AUTHOR.

Campbell, M.: Complete Heart Block. Brit. Heart J. 6: 69, 1944.

Complete heart block is most often seen in men in the seventh decade with enlarged hearts and atherosclerosis but no other evidence of gross heart disease. Four-fifths of our patients were men. Most (45 per cent) were between 60 and 69 years of age, and 84 per cent were over 50 years of age at the onset of complete block.

Syphilitic and rheumatic heart diseases were, between them, responsible for only a little over 10 per cent of the cases. Other myocardial disease was responsible in 75 per cent, or in 86 per cent if the group of congenital cases was excluded, this being the second commonest cause (13 per cent). Cardiac enlargement with no other signs than atherosclerosis of the aorta and often of peripheral arteries was the evidence of myocardial disease in nearly half these cases, high blood pressure, angina pectoris, or congestive failure being present in the other half. In the ten cases with high blood pressure, the average figure was 225/108. In the others, the systolic pressure was above and below 160 in equal numbers, and the average figures for these two groups were 194/81 and 137/73. Thus, in the latter, the pulse pressure was only slightly raised, but in the former and in those with high blood pressure, the pulse pressure averaged 115. The reasons for this have been discussed.

The heart rate was usually between 28 and 40 and averaged just under 35 (excluding congenital cases where it was generally 40 to 56).

Heart block may be of very varied types; it may be: (1) complete, (2) partial; 2:1, or more rarely 3:1 or 4:1, (3) partial with dropped beats only; including regular 4:3, 3:2, etc., or occasional dropped beats, or (4) latent, with a prolonged P-R interval only.

Complete heart block is a serious lesion, though some patients, especially some of those under 40 years of age, live for many years in reasonably good health. There were 50 cases followed for more than 2 years or until their death; 34 were

dead after an average period of 2.5 years; 16 were alive after an average period of 6 years or 4.5 years if two exceptional cases were excluded. Of the former, 19 died in less than 2 years, 14 in from 2 to 6 years, and 1 after 12 years. Of the latter, the period of observation was from 2 to 6 years in 10, and from 7 to 20 years in the other 6 cases.

Stokes-Adams attacks were present in half the patients with complete heart block. When they were present they were one of the earliest if not the first significant symptom of heart block in three-fourths of the cases. In those without Stokes-Adams attacks, dyspnea or attacks of faintness or dizziness were the main presenting symptoms.

Stokes-Adams attacks were no more common in those who had *recorded* latent heart block than in those without. A known change of rhythm at times other than those of the attack does makes Stokes-Adams more likely, but not as much as might be expected (64 against 32 per cent).

The prognosis was considerably worse in those with Stokes-Adams attacks, the results in the patients traced being:

	Alive	Dead
With Stokes-Adams attacks	6	24
Without Stokes-Adams attacks	10	10

The method of dying was even more strikingly different: of the patients with Stokes-Adams attacks, 61 per cent died suddenly, presumably in attacks; of those without Stokes-Adams attacks, only one was known to have died suddenly, and 50 per cent died with failure. If, when a patient is first seen with complete heart block, he has not had a Stokes-Adams attack, the risk of such an attack developing, or of his dying suddenly, is not great, and with each month that has passed the risk becomes still less.

It is important to realize that Stokes-Adams attacks may occur with paroxysmal heart blocks (complete) and the paroxysms may be of short duration after the attacks and may easily be missed. Otherwise attacks that are true Stokes-Adams attacks will remain unexplained.

AUTHOR.

Cossio, P., and Berconsky, I.: The First Heart Sound and Auricular Fibrillation. Rev. argent. de cardiol. **10**: 283, 1943.

The heart sounds were studied by auscultation and graphic records in five patients during periods of auricular fibrillation and sinus rhythm. It was found that, when auricular fibrillation was present, the first sound was of greater intensity and appeared later in relation to the beginning of the QRS group of the electrocardiogram.

The greater intensity of the first heart sound during auricular fibrillation is explained if due consideration is given to the origin of the first sound, fundamentally valvular, and to the preponderance role of the initial tension of the A-V valves in determining its intensity.

AUTHORS.

Thomas, C. B.: The Significance of Electrocardiographic Abnormalities in Young Adults. Bull. Johns Hopkins Hosp. **74**: 229, 1944.

There are a number of physiologic mechanisms which may alter the electrocardiogram, sometimes to an abnormal degree. In the age groups in which degenerative disease of the myocardium is rare, there is greater likelihood that a given electrocardiographic abnormality is a physiologic variant than evidence of a pathologic lesion. Until the limits of normal variation in the human electro-

cardiogram have been much more thoroughly explored, the diagnosis of heart disease in young persons should seldom be based on the electrocardiographic findings alone, in the absence of clinical manifestations.

AUTHOR.

Zimmerman, S. L.: Transient T-Wave Inversion Following Paroxysmal Tachycardia. J. Lab. & Clin. Med. 29: 598, 1944.

One case of supraventricular tachycardia and two cases of ventricular tachycardia followed by T-wave inversion in multiple leads, persisting for a variable period of time and not associated with myocardial infarction, are presented.

The importance of correct evaluation of these changes is stressed.

The role that quinidine played is discussed. It does not appear to have been of etiological importance.

Certain differential electrocardiographic findings are discussed, and their importance in excluding myocardial infarction is stressed.

Persistent inversions of T waves following tachycardias are not necessarily of ominous prognostic import.

AUTHOR.

Davies, J. N. P., and Fisher, J. A.: Coarctation of the Aorta, Double Mitral A-V Orifice, and Leaking Cerebral Aneurysm. Brit. Heart J. 5: 197, 1943.

The case is reported of a male, aged 17 years, with coarctation of the aorta and other congenital defects. He developed a cerebral hemorrhage from a berry aneurysm, and made a complete recovery from this, only to die later from a rupture of the aorta.

The autopsy revealed that, in addition to the coarctation of the aorta and associated defects of elastic tissue, there was a double mitral valve. The probable counterpart during life of this rare anomaly was a presystolic or diastolic murmur in the mitral area.

The relationship of these defects is briefly discussed.

AUTHORS

Baer, S., and Frankel, H.: Studies in Acute Myocardial Infarction. III. Diagnosis and Location of the Infarct by Electrocardiogram. Arch. Int. Med. 73: 286, 1944.

The diagnosis and location of the infarct were considered in 378 cases of acute myocardial infarctation. Electrocardiograms taken in 321 cases revealed the presence of infarction in 94 per cent. On electrocardiographic study alone, 52 per cent of the infarcts were found to be anterior and 34 per cent posterior. Of 74 patients coming to necropsy, 70 per cent had anterior, 23 per cent posterior, and 7 per cent anteroposterior infarction.

Anterior myocardial infarctions are more frequent and more serious than posterior infarctions. Infarction of the anterior wall of the left ventricle is more apt to be missed by electrocardiograms than posterior involvement. Electrocardiographic diagnosis and location of the infarction are highly accurate.

AUTHORS.

McHardy, G., and Browns, D. C.: Life Expectancy After an Attack of Myocardial Infarction. Report of a Case of Survival for Nineteen Years After Coronary Thrombosis. Arch. Int. Med. 73: 290, 1944.

The authors report the present case as the first instance of myocardial infarction due to coronary thrombosis in which there was electrocardiographic confirmation at the onset, and in which the patient lived for so long a time—nineteen

years and thirty days from the initial occlusion until his death, from thrombosis. Both the initial and the terminal attack were confirmed by autopsy.

AUTHORS.

Harrison, T. R.: Clinical Aspects of Pain in the Chest. I. Angina Pectoris. Am. J. M. Sc. 207: 561, 1944.

An analysis of seventy-seven patients with angina pectoris has been made, with particular reference to the characteristics of the pain and its relationship to various body functions.

The pain was felt in the substernal *location* in only about one-half the patients. Pain entirely limited to the periapical, axillary, or abdominal regions did not occur in any case.

The *duration* of the pain was usually a few minutes only, rarely longer than one-half hour. No patient had pain lasting for a few seconds only.

Pain of great *intensity* was exceptional, the discomfort being mild or minimal in more than one-half the patients.

The discomfort was constrictive or heavy in *character* in only about 50 per cent of the cases. Frequently, the pain was of an aching quality; burning discomfort was occasionally found; while lancinating pain was encountered in only one subject.

In addition to the generally recognized "trigger" factors of exertion, eating, emotion, and cold, the recumbent posture and glucose deficiency were found to be common precipitating causes of the seizures. Anginal attacks with typical electrocardiographic changes may be induced by spontaneous hypoglycemia in patients who have no seizures with severe effort and no evidence of structural cardiac disease. The act of eating may precipitate anginal attacks in certain patients and may prevent the attacks in other subjects.

Pain induced by the sitting or standing position or aggravated by breathing, coughing, or swallowing can usually be safely ascribed to disorders other than angina pectoris.

In the diagnosis of angina pectoris the most important features are: the history of relationship to effort, the short duration of the pain, and the demonstration that the amount of muscular effort required to induce the pain is increased by nitroglycerin.

A large percentage of patients with angina pectoris also suffer from chest pain due to other disorders. Such disorders may either be related to angina pectoris (as in the case of myocardial infarction and reflex disturbances of the skeletal system) or unrelated to it (as in the case of gall bladder disease, hiatal hernia, esophageal spasm, and so forth). Because of the frequent coexistence of the two causes of chest pain, one of them may be overlooked unless unusual care is employed in obtaining the history.

Occasional patients—about 10 per cent in this series—may have anginal attacks which have never been related to effort. Among the causes of such attacks are status anginosus ("coronary insufficiency," "preinfarction angina") ectopic tachycardia, spontaneous hypoglycemia, and conditions such as intermittent claudication, congestive failure, and undue anxiety about the cardiac condition, which induce the patient to lead an unusually sedentary life. It is in this group of patients that the greatest diagnostic difficulty is likely to be encountered.

AUTHOR.

Dodge, K. G., Baldwin, J. S., and Weber, M. W.: The Prophylactic Use of Sulfanilamide in Children With Inactive Rheumatic Fever. J. Pediat. 24: 483, 1944.

Eighty-eight children and adolescents with quiescent rheumatic disease were given from 1 to 2 Gm. of sulfanilamide daily throughout the winter and spring months for a total of 181 patient-seasons.

One hundred and one rheumatic children were observed as controls for 138 patient-seasons.

In the group receiving sulfanilamide, in some cases for as many as four seasons, toxic drug reactions were minimal. The drug was not discontinued permanently in any case for such a reaction.

During the period of the study, there were, in the control group, fifty-four Group A hemolytic streptococcal infections, an incidence of 39 per cent. There were nineteen definite major rheumatic relapses (with two deaths) and seven mild or possible relapses. In three children, the rheumatic process remained active throughout the period of observation, and there was one death from subacute bacterial endocarditis.

In contrast to this, only five hemolytic streptococcal infections occurred in the group of children receiving sulfanilamide prophylaxis, an incidence of 2.7 per cent. Two children, or 1.1 per cent of the patient-seasons of prophylaxis, developed definite rheumatic relapses while taking the drug regularly. Two other children with severely damaged hearts died of congestive failure without evidence of streptococcal infection or active rheumatic disease. Two children with recently active rheumatic fever showed signs of increasing rheumatic activity within two weeks of starting the drug. The remainder of this group of children remained free of streptococcal infection and rheumatic relapses.

Some of the problems of the administration of a sulfonamide prophylactically have been discussed.

Based on this study and reports in the literature, the effectiveness of sulfonamide prophylaxis in quiescent rheumatic fever is established, and it should be applied more widely among groups of highly susceptible individuals.

AUTHORS.

Davis, D. B., and Rosin, S.: Rheumatic Fever and Rheumatic Heart Disease in Los Angeles Children. J. Pediat. 24: 502, 1944.

The cases of 157 patients with childhood rheumatic disease admitted to the Los Angeles County Hospital over a five-year period are analyzed and discussed. The following salient findings bear emphasis:

The relatively low incidence of rheumatic disease, as determined by this survey, is consistent with the findings of similar studies carried out in other cities with subtropical climates.

Chorea seems to occur with much less frequency in this area than in eastern population centers.

No significant variation in seasonal incidence is noted.

An analysis of temperature, rainfall, and relative humidity permits no correlation between these factors and the incidence of the disease in this area.

Familial incidence in this series is negligible.

Two-thirds of the patients were born and raised in this community. Almost 80 per cent of those born out of California lived in the Los Angeles areas over one year before the onset of rheumatic disease. These facts would certainly tend to discredit the commonly held belief that the majority of the patients with rheumatic infection encountered here are migrants from eastern or northern states.

The mortality in this series was 9.5 per cent. Brief summaries are presented of all cases that proved fatal.

AUTHORS.

Thompson, R. B.: A Case of Myxoma of the Left Auricle. Brit. Heart J. 6: 23, 1944.

A case of myxoma of the left auricle with congestive heart failure and sudden death is presented with an autopsy report.

AUTHOR.

Evans, W.: The Heart in Myotonia Atropica. Brit. Heart J. **6**: 41, 1944.

Examination of the heart in thirteen cases of myotonia atrophica has shown that the presence of cardiovascular signs may help in the earlier diagnosis of the condition.

The pulse is often small and occasionally infrequent. The blood pressure is sometimes very low. The first heart sound in the mitral area commonly shows splitting, and sometimes triple rhythm may appear from addition of the fourth heart sound, this depending on the degree of elongation of the P-R period.

The changes that commonly characterize the electrocardiogram include elongation of the P-R period, low voltage of the P wave, slurring of the QRS complex, and left axis deviation.

The size of the heart varies so that it may be normal or may appear small, but in the presence of considerable lengthening of the P-R period, moderate enlargement takes place.

AUTHOR.

Pietrafesa, E. R.: Observations on Two Cases of Arteriovenous Communication. Rev. argent. de cardiol. **10**: 302, 1943.

A study was made of the circulatory changes which appeared in two patients with an arteriovenous aneurysm of the right leg, when the femoral artery was compressed at the level of the Poupart's ligament. The heart rate, the oscillatory index of the limb arteries, the different phases of the cardiac cycle, arterial and venous pressure, cardiac output, heart size, electrocardoigram, and heart sounds were investigated.

It is concluded that the circulatory changes produced by compressing the artery of an arteriovenous aneurysm are not always the same. The size of the arteriovenous fistula, the time of its establishment and the circulatory compensation which follows are among the factors which determine the circulatory response to compression of the artery.

AUTHOR.

Langley, G. F.: Repair of Ruptured Popliteal Artery, With Note on Heparin Therapy After Arterial Suture. Brit. J. Surg. **31**: 161, 1943.

A case of rifle bullet wound of the popliteal vein with delayed rupture of the popliteal artery has been described. Suture of the popliteal artery after rupture of an arterial hematoma was successfully performed. External, popliteal nerve palsy developed as a secondary complication, but the patient recovered from this.

Heparin administration probably contributed to the saving of the limb. It is suggested that heparin should be administered in a continuous saline drip, as it is unlikely to be effective by intermittent intravenous injection; the accepted dosage of heparin may be too small, and it is necessary for repeated examinations of the clotting time to be made.

AUTHOR.

Bloom, N., and Walker, H.: Nodal Rhythm and Bundle Branch Following Aspirin Hypersensitivity. J. Lab. & Clin. Med. **29**: 595, 1944.

Aspirin is an excellent analgesic and, considering its enormous consumption, only occasionally causes any severe reactions in human beings. This case is an example of very unusual sensitivity to the drug. Anaphylactic shock with transient nodal rhythm and bundle branch block occurred after the ingestion of five grains of aspirin. Within twenty-four hours, all of these phenomena had disappeared.

AUTHORS.

American Heart Association, Inc.

1790 Broadway at 58th Street, New York, N. Y.

THE American Heart Association is the only national organization devoted to educational work relating to diseases of the heart. Its activities are under the control and guidance of a Board of Directors composed of thirty eminent physicians who represent every portion of the country.

A central office is maintained for the coordination and distribution of important information. From it there issues a steady stream of books, pamphlets, charts, films, lantern slides, and similar educational material concerned with the recognition, prevention, or treatment of diseases of the heart, which are now the leading cause of death in the United States. The American Heart Journal is under the editorial supervision of the Association.

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